Multidisciplinary Management of Gastroesophageal Reflux Disease

Sebastian F. Schoppmann
Martin Riegler
Editors

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ISBN 978-3-030-53750-0 ISBN 978-3-030-53751-7 (eBook)
https://doi.org/10.1007/978-3-030-53751-7

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

“Not for nothing rivers
Flow in dryness.”

Friedrich Hölderlin; *The Ister*

"This book is dedicated to our families, friends, and teachers and to all our patients, from whom we are allowed to learn and borrow a better understanding to improve the management of the disease."

Meeting the Qualities of the Tube: Be Rapid, Essential, and Effective

Dear reader,

Welcome to this book entitled *Multidisciplinary Management of Gastroesophageal Reflux Disease (GERD)*.

It deals with one of the most important and most frequent lifestyle diseases of our modern world, i.e., GERD. In addition, the book aims to meet and synchronize the most essential demands of our modern time. It will offer *rapid* retrieval of *essential* information required for *effective* disease management.

The book summarizes our novel understanding of GERD and how this novel understanding translates into modern disease management and cancer prevention. Due to the unique anatomical, histopathological, and pathophysiological qualities and characteristics of the esophagus, the book offers a *multidisciplinary management* of GERD, including histology, physiology, radiology, ENT, pulmonology, gastroenterology, endoscopy, surgery, palliation, and interventional medicine.

We hope that the book will foster a cause-directed GERD management, which seeks to outbalance the failure of the function of the antireflux mechanism within the lower end of the esophagus. Conceptually novel GERD diagnosis aims to assess the extent of the failure of the lower esophageal sphincter (LES) and the grade of dys-geometry of the anchorage of the lower esophagus within the diaphragmatic hole. Multidisciplinary therapy aims to restore esophageal function and to compensate or eliminate multiple somatic manifestations of reflux, including premalignant *Barrett's esophagus*. Thus, the spectrum of therapies for symptom control and cancer prevention includes lifestyle, medical, and interventional measures (novel endoscopic and surgical therapies, oncological surgery, and palliation of esophageal cancer).

In addition, the book presents fascinating novel tools for the diagnosis and therapy of GERD including endoscopic techniques (mucosal resection, EMR; radio frequency ablation, RFA), novel antireflux surgery (endostim, magnetic sphincter augmentation LINX, radio frequency STRETTA, etc.). Special attention is focused on the management of Barrett's esophagus (BE), where reflux induces the formation of a *precancerous tissue* in the lower end of the esophagus.

The multidisciplinary approach uniquely allows to orchestrate an *individually tailored therapy* including different specialties involved in the management of GERD and BE (ENT, gastroenterology, pathology, radiology, pathophysiology, surgery, etc.).

We thank the outstanding panel of expert authors for their exceptional contributions and Springer for giving us the opportunity to publish the book and thus being allowed to bring it to the attention of the reader.

Taken together, we hope that the book helps you to have more fun and success in managing your GERD and BE patients and to gain a better understanding for the causes underlying this modern lifestyle disease.

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1 Pathophysiology of Lower Esophageal Sphincter Damage: A New Method of Diagnosis of Gastroesophageal Reflux Disease

Parakrama Chandrasoma

Pathology has no clinical value at the present time in the diagnosis and management of early gastroesophageal reflux disease (GERD). Biopsies are not recommended for establishing the diagnosis of GERD. Their only value is in the diagnosis of intestinal metaplasia in the patient with visible columnar-lined esophagus (vCLE), which establishes the diagnosis of Barrett esophagus. It is also necessary for the diagnosis of increasing dysplasia and adenocarcinoma in surveillance biopsies taken from patients with Barrett esophagus.

Barrett esophagus is a late complication of GERD. Its presence indicates that the patient has entered the neoplastic cascade which ends in adenocarcinoma in a small minority of patients. At the present time, there is no ability to prevent progression to neoplasia in Barrett esophagus. The only available course is early diagnosis of significant dysplasia and early adenocarcinoma followed by endotherapy directed as eradicating the neoplastic lesion.

We will only consider GERD in this chapter. We will explore the pathophysiology of GERD through its entire progression from the normal state to severe GERD. This will lead to the proposal of a new pathologic test for lower esophageal sphincter (LES) damage that is based on mucosal changes defined by histology. The new ability to measure LES damage has the potential to open the door to a new method of diagnosis and management of GERD that has the potential to eradicate GERD-induced esophageal adenocarcinoma.

The evidence base in support of the new test is solid, albeit small. Its acceptance requires the removal of two long held and powerful dogmas that presently preclude acceptance of the new method: (a) that cardiac epithelium normally lines the proximal stomach and (b) that the gastroesophageal junction (GEJ) is accurately defined

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_1

by the proximal limit of rugal folds and/or the end of the tubular esophagus. The evidence shows clearly that these are both false even as they continue to be accepted.

What is being proposed is revolutionary.

1.1 The Present Status of GERD and Its Management

Gastroesophageal reflux disease (GERD) is regarded as a chronic progressive disease. When defined by the presence of symptoms that reach a point where they are considered troublesome [1], 20–40% of the population has GERD. Approximately 70% of these patients are well controlled throughout life with proton pump inhibitors (PPIs). Their disease does not seem to be progressive although some dose escalation may be needed for control.

From this perspective, progression of GERD is limited to the approximately 30% of GERD patients in whom PPI therapy fails to control symptoms (Fig. 1.1). There is no ability or attempt to prevent the progression of this 30% of GERD patients into the stage of refractory GERD defined by treatment failure. Patients who fail to be controlled with PPIs live a life whose quality is compromised to varying degrees by their symptoms. It is only when they reach this stage, defined by failure of PPIs to control symptoms or when they develop alarm symptoms such as dysphagia, that endoscopy is indicated [2].

From the different perspective of endoscopy, GERD progresses from no visible endoscopic change to erosive esophagitis of increasing severity (Los Angeles grade A to D), visible columnar-lined esophagus (vCLE), Barrett esophagus (defined as vCLE with intestinal metaplasia in the USA), and through increasing dysplasia to adenocarcinoma.

Biopsy is not recommended in patients who do not have an endoscopic abnormality [2]. Biopsy of the endoscopically normal squamous epithelium may show histologic changes of reflux, but these are not sufficiently sensitive or specific to have practical value.

Biopsy of the "normal" squamocolumnar junction (SCJ) is not recommended in patients without vCLE, although it is known that a small but significant number of patients will have intestinal metaplasia if biopsies are taken [3].

Endoscopy in the patient who has failed PPI therapy changes management only in the patient with Barrett esophagus, who enters an endoscopic surveillance program aimed at detecting early neoplastic changes (Fig. 1.1). In patients without Barrett esophagus, endoscopy provides little, if any, useful information that impacts symptom control with PPIs. Barrett esophagus has no effective medical treatment. Progression to dysplasia and adenocarcinoma cannot be effectively prevented [4].

Symptoms of GERD and endoscopic findings are not concordant. A person without symptoms of GERD can have long segment Barrett esophagus or present with an advanced GERD-induced adenocarcinoma. Conversely, a patient with symptoms of GERD can be endoscopically normal (nonerosive reflux disease). Treatment of GERD with PPIs can heal erosive esophagitis without completely resolving GERD symptoms [2]. Patients with NERD are more resistant to symptom control with PPI than those with erosive esophagitis [2].

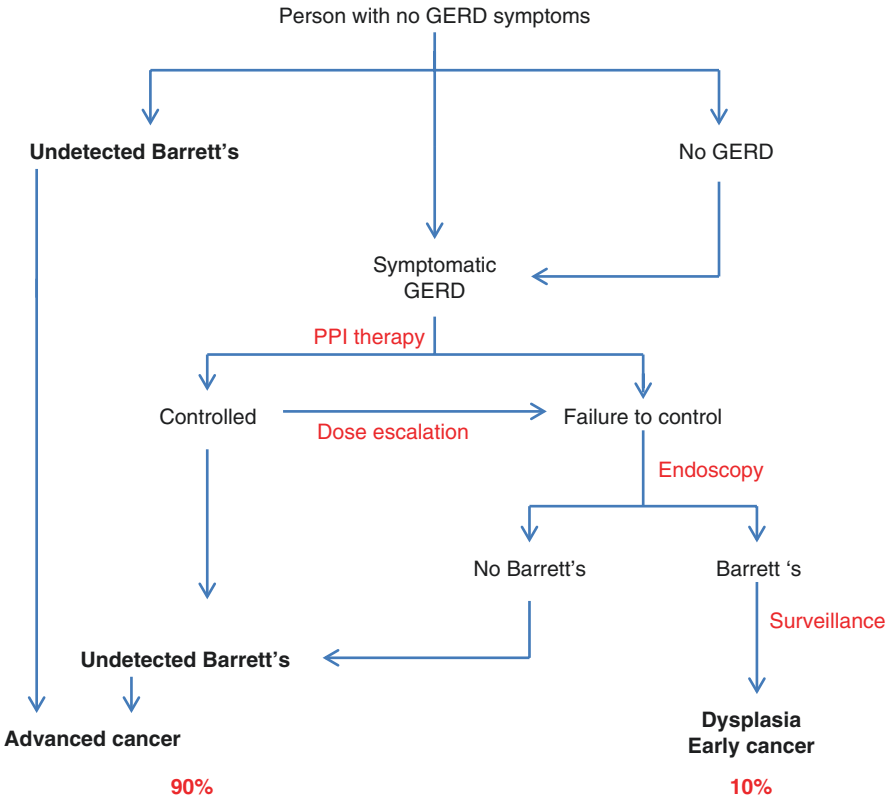


Fig. 1.1 The failure of the present treatment algorithm of GERD to prevent mortality from esophageal adenocarcinoma. Endoscopy is limited to patients who fail medical therapy, and surveillance is limited to those patients who have Barrett esophagus at endoscopy. Ninety percent of adenocarcinomas occur in asymptomatic people, patients well controlled by PPI, and people that do not have Barrett esophagus at endoscopy. Only 10% are found in early stages of cancer and can be treated effectively with a mortality of <30% compared to 90% for advanced cancer

There is no practically effective method of diagnosis of GERD in a patient presenting with symptoms that are suspected to be the result of GERD. As a result, all patients receive empiric acid suppressive treatment with the sole objective of symptom control. A positive empiric test of PPI therapy is commonly used to confirm the symptom-based diagnosis of GERD [2].

There is no symptom complex or test at present that can accurately predict which GERD patient under empiric treatment will progress to failure of PPI therapy in the future. Failure is recognized only when maximum PPI therapy fails to control symptoms.

There is no symptom complex or endoscopic finding short of Barrett esophagus that can predict with sufficient accuracy to warrant screening that a GERD patient will develop adenocarcinoma in the future. Screening for Barrett esophagus is not recommended [3].

This treatment algorithm therefore precludes any method that can prevent the progression of GERD to its severe end points of treatment failure and adenocarcinoma. When the end point of severe GERD is compromised quality of life, surgical sphincter augmentation and fundoplication offers the only hope of control. However, surgery has its own problems and is performed relatively rarely. Many patients who opt to not have surgery continue to live a life that is disrupted by fear of eating, sleep deprivation, and loss of productivity at work [5].

When the end point is advanced adenocarcinoma, hope exists for very few patients and too commonly for a very short period of time (Fig. 1.1). Only 10% of patients developing adenocarcinoma have ever had a diagnosis of Barrett esophagus. These patients are detected with early stage cancer that is amenable to endoscopic therapy, which is often curative and obviates the need for esophagectomy, chemotherapy, and radiation. The other 90% of patients have a dismal outcome with a 5-year survival of around 15%.

This is a sad commentary of our present management of GERD. We have abandoned the hallowed principles of early diagnosis and prevention in favor of an illogical and unrealized hope that PPIs will cure the disease. We simply permit the development of severe GERD and then struggle with few good answers to prevent the inevitable impaired quality of life and progression to adenocarcinoma in a highly significant minority of patients with GERD.

There is no attempt to control progression of GERD. There is no attempt to prevent adenocarcinoma or its premalignant state, Barrett esophagus. There is no attempt to prevent the state of misery associated with GERD that becomes refractory to PPI therapy.

A revolution is essential if there is to be any control of the ever-increasing incidence of adenocarcinoma [6]. This is the first attempt at such a revolution.

1.2 Progression of GERD with Empiric PPI Therapy

The best available scientific prospective study of long-term outcomes associated with treating symptomatic GERD with acid suppressive medical therapy is the ProGERD study [7]. Six thousand two hundred fifteen patients over 18 years old with the primary symptom of heartburn were enrolled into this prospective multicenter open cohort study in Europe. The study was largely conducted under the auspices of AstraZeneca, makers of esomeprazole, which makes any result that suggests a negative effect of PPI therapy highly credible.

All patients underwent an index endoscopy done in selected centers by endoscopists who received special training. Endoscopic findings were recorded and the patients were given 4–8 weeks of PPI therapy with assessment of symptoms control and repeat endoscopy to assess healing. They were then sent back to their primary care physicians for continuation of empiric acid suppressive treatment at their discretion. Treatment used during follow up and symptom control was monitored by questionnaires. 2721 of this cohort of patients reported to the study centers for repeat endoscopic assessment at 5 years.

At the initial endoscopy, the distribution of endoscopic changes of these 2721 patients was as follows: nonerosive disease, 1224; erosive disease LA A/B, 1044; erosive disease LA C/D, 213; 240 (8.8%) patients had vCLE. (Note: vCLE was reported as "Barrett esophagus, endoscopic" and "Barrett esophagus with histologic confirmation," the latter with intestinal metaplasia). The patients with vCLE at the initial endoscopy were not included in this study.

Reversal and prevention of progression of erosive esophagitis at 5 years was impressive. Of the1041 patients with nonerosive disease at baseline, 784 remained nonerosive, 248 progressed to LA A/B, and 9 to LA C/D erosive disease. Of the 918 patients with LA A/B erosive disease at baseline, 578 had reversed to nonerosive disease, 331 remained LA A/B, and 9 had progressed to LA C/D erosive disease. Of the 188 patients with LA C/D erosive disease at baseline, 94 now had nonerosive disease, 78 had LA A/B, and 16 stayed at LA C/D erosive disease. Over a period of 5 years, the number of patients with severe erosive esophagitis had decreased from 188 to 34. Regular intake of PPI reduced the likelihood of progression compared with on-demand PPI or other therapy. The severity of symptoms at baseline was not a predictor of progression to severe erosive esophagitis. It could reasonably be concluded that PPI therapy was highly effective in healing erosive esophagitis.

In contrast, 241 (9.7%) patients who did not have vCLE initially had developed this at 5 years. These patients who progressed included 72/1224 (5.9%) who originally had NERD, 127/1044 (12.1%) with LA grade A/B, and 42/213 (19.7%) with LA grade C/D erosive esophagitis. The factors significantly associated with progression to vCLE at 5 years were: (a) female gender, which had a negative association ($p = 0.041$); (b) alcohol intake ($p = 0.033$); (c) erosive esophagitis compared with NERD ($p < 0.001$); and (d) regular PPI use ($p = 0.019$).

This data shows that empiric PPI therapy titrated to control symptoms in the primary care setting heals erosive esophagitis effectively, but simultaneously results in an endoscopic progression to vCLE with and without intestinal metaplasia. Whether PPI therapy causes this conversion is unproven. However, the study data proves that nearly 10% of the GERD population under empiric acid reducing treatment will progress from not having vCLE to vCLE within 5 years. A patient without vCLE is not considered at present to be at risk for GERD. This means that 10% of patients being treated by standard treatment for GERD in the community progress from a state that is not considered at risk for malignancy (i.e., no vCLE) to a premalignant state (i.e., Barrett esophagus).

When one considers that 20–40% of the population have symptomatic GERD, 10% translates to an absolute number that easily explains why GERD-induced adenocarcinoma has increased sevenfold in the past four decades [6].

1.3 Value of Pathology in the Diagnosis of GERD

Pathologic criteria for diagnosis of GERD are presently limited to changes in the squamous epithelium of the esophagus that result from exposure to gastric contents. Reflux esophagitis is characterized by intercellular edema (dilated intercellular

spaces), basal cell hyperplasia, papillary elongation, and infiltration by eosinophils and neutrophils. These changes do not have the necessary sensitivity or specificity for the diagnosis of GERD. As such, histologic examination of biopsies has no practical value in the diagnosis of GERD.

Pathologic criteria do not exist at present for assessment of the lower esophageal sphincter (LES). In this chapter, we will develop a new set of pathologic criteria that can define the presence and extent of damage to the abdominal segment of the LES (a-LES). We will also explore how this simple histologic test for a-LES damage can transform the future management of GERD.

1.4 A Proposed New Objective in the Management of GERD

The present treatment algorithm for GERD (Fig. 1.1) can be described as totally reactive. There is no defined objective aimed at detecting or preventing any cellular change that may be a harbinger of adenocarcinoma. We simply wait for symptoms that are "troublesome" to begin empiric PPI therapy [1]; then wait for failure of PPI therapy to perform endoscopy [2]; and then wait for the occurrence of high-grade dysplasia and adenocarcinoma. The only proactive event in this algorithm that improves outcomes is Barrett esophagus surveillance, results in earlier detection of adenocarcinoma.

Even worse, most physicians convince themselves that PPI therapy is a wonderful method of treating GERD that brings comfort to millions of GERD sufferers. This is true. However, we hide and ignore the greatest increase of a specific cancer type in the history of medicine that has concurrently occurred while patients are being treated with increasingly effective acid reducing drugs [6].

In this chapter, we will attempt to change the present outcomes of GERD with a new approach based on the development of a new understanding of GERD based on the pathogenesis of progression of a-LES damage.

It is well known that GERD is the result of LES damage. As such, focus on LES damage attacks the problem at its root. The primary objective of the new approach is to turn the curve of increasing incidence of adenocarcinoma downward all the way to zero. A secondary objective is to prevent failure of medical therapy.

1.4.1 Defining a Criterion of Irreversibility: vCLE

The first step in preventing adenocarcinoma is to recognize the point of irreversibility that signals the inability to prevent progression to adenocarcinoma. In GERD, at this point in time, that point of irreversibility is the occurrence of vCLE. In the United Kingdom, vCLE defines Barrett oesophagus [8]. In the USA and Europe, intestinal metaplasia is required for the diagnosis of Barrett esophagus.

Medical treatment does not reverse vCLE or prevent its progression to intestinal metaplasia, increasing dysplasia and adenocarcinoma. Present medical treatment of GERD therefore commits 10% of all patients to irreversibility every 5 years [7].

The advantage with defining irreversibility in GERD by the presence of vCLE is that there is no evidence that any patient who does not have vCLE progresses to adenocarcinoma. If we prevent vCLE, we will prevent adenocarcinoma.

It can be reasonably argued that the person who is endoscopically normal with intestinal metaplasia at the normal SCJ is at risk for adenocarcinoma of the "gastric cardia." However, present management guidelines recommend that such patients with GERD should not undergo biopsies because the risk of cancer in patients who have intestinal metaplasia is unknown [2]. The argument, therefore, has no practical merit at this time. It may change in the future if an increased cancer risk is defined in this group. If and when that happens, preventing intestinal metaplasia at the SCJ in the endoscopically normal person will become necessary.

The detection of vCLE requires endoscopy. The present management guidelines delay endoscopy to the point of treatment failure. At this point a significant number of patients will already have vCLE. If endoscopy is performed proactively without waiting for treatment failure, as was done in the Pro-GERD study, 240/2721 (8.8%) patients would already have vCLE [7]. In addition, the following endoscopic findings were predictive of progression to vCLE in the next 5 years: (a) presence of erosive esophagitis with risk increasing to 19.7% in patients with severe erosive esophagitis [7] and (b) presence of intestinal metaplasia in a biopsy taken from the SCJ of an endoscopically normal patient; such patients had a 25% risk of progression to vCLE within 5 years [9]. The patients in the Pro-GERD study had well-established GERD, often with severe symptoms and a long duration [7]. It is probable that endoscopy performed at the onset of GERD would have a lower prevalence of vCLE.

In the Pro-GERD study, the non-endoscopic findings that were significantly associated with progression to vCLE in GERD patients under medical therapy were male gender, alcohol use, and regular PPI use.

None of the non-endoscopic criteria that are predictive for development of vCLE within 5 years listed above are indications for endoscopy in the GERD patient. The indication remains the occurrence of treatment failure. The main reason for this is the lack of any desire to prevent vCLE in the minds of the medical community. To them, vCLE is simply another inevitable event in the course of GERD that occurs in a minority of GERD patients. The fact that it is a cellular change whose end point is a lethal malignancy is ignored.

This is a nihilistic attitude that permits conversion of the patient without risk to one whose progression to adenocarcinoma becomes inevitable. The only excuse for this attitude is that cancer is rare in GERD patients. With the sevenfold increase in the incidence of GERD-induced adenocarcinoma over the past four decades [6], this excuse has become increasingly lame and unacceptable.

If the presence of vCLE is recognized as the point of irreversibility in GERD, there can be a new objective of management of the GERD patient: *the prevention of progression to vCLE.*

This would then provide an incentive and demand for earlier endoscopy before failure with empiric treatment with PPI in the patient with GERD. Early endoscopy presently has the ability only to recognize the presence of vCLE and predict its

occurrence within the next 5 years by the presence of severe erosive esophagitis (19.7%) and intestinal metaplasia at the normal SCJ (25%). Successful repair of the damaged lower esophageal sphincter (LES) in the patient with a high risk of vCLE in 5 years has a high probability of preventing vCLE.

These reasons for early endoscopy are presently not justified because of the cost associated with increasing the number of endoscopies. However, it emphasizes the fact that any push to prevent adenocarcinoma must change the indications for endoscopy to an earlier stage in the progression of GERD. This will only happen if a new and more accurate method of predicting progression of GERD to vCLE becomes available. The new histologic measure of LES damage that we propose can be that test.

1.4.2 The Cause of vCLE

To be effective in preventing vCLE, we must identify its cause. It is certain that vCLE is the result of exposure of the esophagus above the endoscopic GEJ to gastric contents as a result of reflux. As such, it is also certain that if reflux can be prevented, vCLE will not occur.

There is strong evidence that the risk of vCLE increases with increasing severity of reflux (demonstrated by objective evidence of acid exposure by a pH test), increasing duration of reflux, male gender, regular PPI therapy, and possibly alcoholism and smoking. Nason et al. [10], showed that the prevalence of Barrett esophagus was higher in patients whose symptoms were controlled with PPI therapy. They suggested that the present practice of waiting for treatment failure was irrational if the objective for endoscopy was the detection of Barrett esophagus.

The most dominant factors in the etiology of vCLE are the severity and duration of reflux. Patients with Barrett esophagus are known to have a higher prevalence of an abnormal pH test than any other category of GERD. There is no specifically defined level of abnormality in the pH test or a specific number of years of reflux that correlates with the occurrence of vCLE. If the objective is preventing vCLE, success will demand intervention at the earliest practical time after the onset of reflux. For prevention of vCLE to be certain, intervention must occur before any significant reflux occurs into the thoracic esophagus.

From a practical standpoint, it is necessary that we can identify criteria that separate very low and high risk of impending and future vCLE by some defined severity and/or duration of reflux. This is not possible by presently available tests. We will propose that the new test of LES damage provides accurate criteria for predicting future vCLE.

It is certain that the severity of reflux into the thoracic esophagus correlates with the frequency of LES failure, which in turn correlates with the severity of LES damage. In relation to our objective of preventing vCLE, this recognition establishes a new more practical objective: *prevention of reflux into the thoracic esophagus that is severe enough to cause vCLE.*

1.5 The Lower Esophageal Sphincter

One of the great obstacles to the study of GERD is the absence of a pathologic method of assessing the LES by pathology at autopsy and resection specimens. Careful study of the region has identified complicated arrangement of the muscle fibers that may represent the LES [11], but these cannot be translated into routine pathology practice. The LES can only be defined and measured by manometry (Fig. 1.2).

The LES acts as a beautifully designed barrier that prevents reflux of gastric contents into the esophagus [12, 13]. The LES pressure is normally >15 mmHg, exceeding the baseline luminal pressure in the esophagus (normally around—5 mmHg) proximally and the baseline luminal pressure in the stomach (normally around +5 mmHg) distally. The LES therefore acts as a valve that effectively prevents reflux along the natural pressure gradient that exists from the stomach into the esophagus (Figs. 1.3 and 1.4).

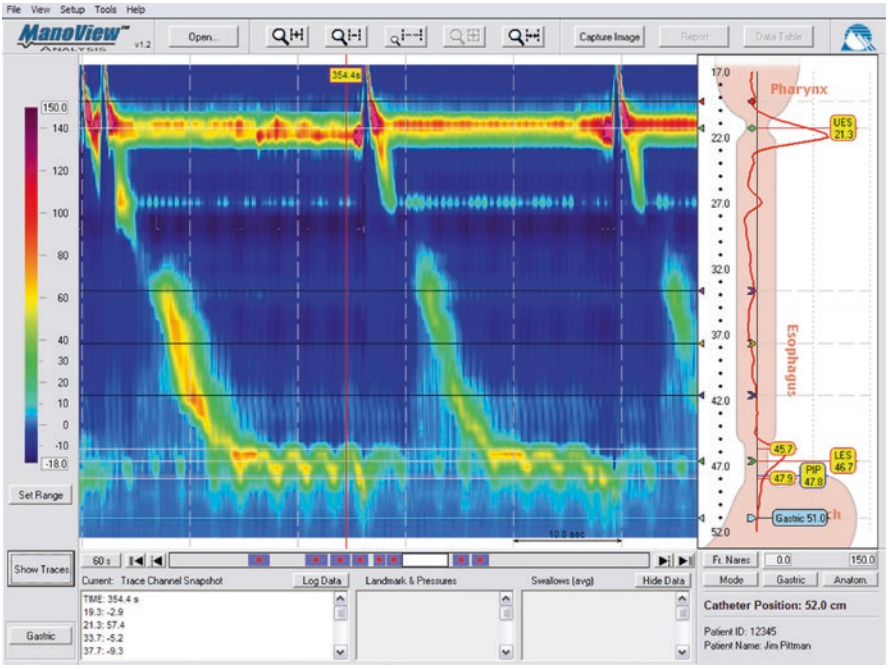


Fig. 1.2 High-resolution manometry showing the esophageal pressure tracing during three swallows. The LES is the high-pressure zone defined by an increase of 2 mm from baseline esophageal pressure at the proximal end and from baseline gastric pressure at the distal end. The LES relaxes during the swallow and regains its resting pressure between swallows

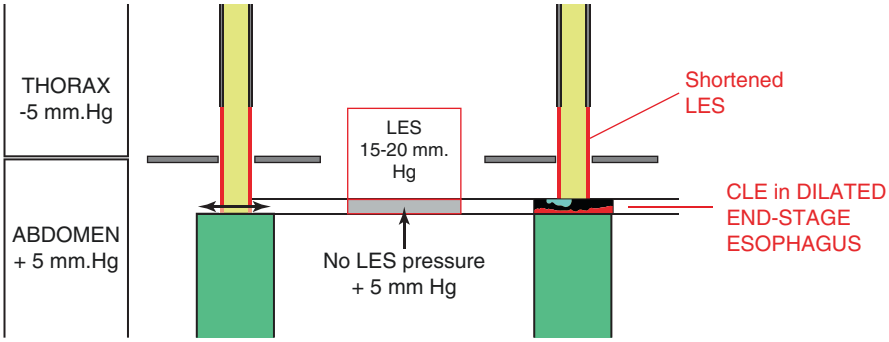
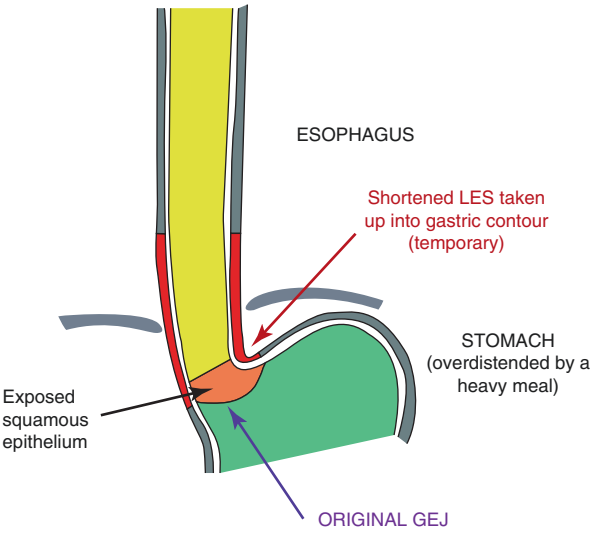


Fig. 1.3 Effect of loss of pressure in the abdominal segment of the LES. The normal resting pressure of the abdominal LES overcomes the positive intraluminal pressure in the abdominal esophagus and maintains the tubal shape of the esophagus. When the LES pressure is lost, the intraluminal pressure causes this part of the distal esophagus to dilate. (NOTE: dilated end stage esophagus was the older term for dilated distal esophagus)

Fig. 1.4 Mechanism of exposure of the squamous epithelium of the distal esophagus to acid. When the stomach overdistends with a heavy meal, the LES shortens, the distal LES becomes effaced, i.e., moves down into the contour of the gastric fundus and the squamous epithelium becomes exposed to gastric contents of the full stomach. There is, at the top of the food column, an acid pocket that meets the descending squamous epithelium



1.5.1 Defining the Normal and Defective LES by Manometry

The functional state of the LES can be defined manometrically by three separate components [12, 13]: its mean pressure, its total length, and the length of its abdominal segment. Manometric studies of asymptomatic subjects indicate that the LES pressure is >15 mmHg, and the total LES length is approximately 50 mm and the length of the abdominal segment (a-LES) is approximately 35 mm.

The criteria that define a defective LES that correlates with the presence of sufficient reflux into the esophagus to produce clinical GERD are [13]: (a) a decrease

in the mean LES pressure to <6 mmHg, (b) a decrease in total LES length to <20 mm, and (c) a decrease in a-LES length to <10 mm. At these levels of LES damage, sphincter failure occurs so frequently that it results in an abnormal pH test and significant exposure of the squamous epithelium in the body of the esophagus to reflux [13]. LES damage defined by these criteria correlate with an increased probability of symptoms of GERD, severe grades of erosive esophagitis, and vCLE.

There is a significant gap between the above criteria that define a normal LES and a defective LES that is associated with abnormal reflux into the esophagus as defined by an abnormal pH test and the presence of clinical GERD. The mean LES pressure must decrease from a normal of >15 to <6 mmHg; the total LES length must decrease from a normal of 50 to <20 mm; and the a-LES length must decrease from 35 to <10 mm before it becomes a criterion of LES failure.

At least part of this gap between a normal and defective LES represents the reserve capacity of the LES. As LES damage increases, its reserve capacity is progressively reduced. However, as long as it is not exhausted, the LES maintains its competence (green zone in Table 1.1).

Table 1.1 Length of a-LES damage (measured by the new test), length of the residual functional a-LES, and their correlation with LES failure and severity of reflux

a-LES damage	Residual a-LESlength	Postprandial a-LESlength	Probability of LES failure	Severity of reflux (% time pH < 4)
zero	35 mm	25 mm	Zero	Zero
> 0 to < 5 mm	30-35 mm	20-25 mm	Zero	Zero
5 - < 10 mm	25-30 mm	15-20 mm	Zero	Zero
10 - < 15 mm	20-25 mm	10-15 mm	Postprandial - rare	> zero to 4.5%
15 - < 20 mm	15-20 mm	5-10 mm	Postprandial - frequent	> zero to 4.5%
20 -25 mm	10-15 mm	0-5 mm	Postprandial – very frequent	> 4.5%
25 -30 mm	**5-10 mm**	**zero**	**Incessant**	**>> 4.5%**
30 -35 mm	**Zero to 5 mm**	**zero**	**Incessant**	**>>> 4.5%**

LES = lower esophageal sphincter; GERD = gastroesophageal reflux disease;
a-LES= abdominal segmentof the lower esophageal sphincterNOTE: Green areas: the LES is competent with damage that is within its reserve capacity.
Orange areas: clinical GERD from onset of symptoms topoint oftransition from postprandial reflux to incessant reflux and an increasing prevalence of vCLE. Red areas: the LES is incompetent with severe reflux and a high prevalence of vCLE;

We assume that the patient has an initial a-LES length of 35 mm, that a heavy meal causes 10 mm of dynamic shortening of the a-LES in the postprandial phase, and that LES failure occurs at an a-LES length of <10 mm

LES lower esophageal sphincter; *GERD* gastroesophageal reflux disease; *a-LES* abdominal segment of the lower esophageal sphincter

NOTE: Green areas: the LES is competent with damage that is within its reserve capacity. Orange areas: clinical GERD from onset of symptoms to point of transition from postprandial reflux to incessant reflux and an increasing prevalence of vCLE. Red areas: the LES is incompetent with severe reflux and a high prevalence of vCLE

This early LES damage cannot be recognized by any present criterion for the diagnosis of GERD: the patient has no symptoms, no endoscopic abnormality, no manometric criteria of a defective LES, and no abnormal pH test. This state where the LES is damaged within its reserve functional capacity can be called "the phase of compensated LES damage." We will show that histologic examination with new criteria can define and measure this early LES damage.

Before the onset of LES damage, all persons have an initial a-LES length that is equal to the length of the abdominal esophagus. Zaninotto et al. [13], reported that the manometric length of the a-LES in 49 asymptomatic volunteers had the following distribution (I have taken the liberty of removing one outlier that had an a-LES length > 50 mm): <10 mm in 1; 10–15 mm in 6; 15–20 mm in 10; 20–25 mm in 17; 25–30 mm in 11; and 30–35 mm in 5 persons.

The manometric measurement of the a-LES at any given point in a person's life after the LES has developed completely can be expressed by the following formula:

$$\text{Initial a-LES length} = \text{manometric a-LES length} + \text{LES damage}$$

This only assumes that the anatomic part of the abdominal esophagus that contains the a-LES does not disappear into thin air when LES pressure is lost.

Manometrically, LES damage is equivalent to loss of pressure. When this occurs at the distal end, it results in shortening of the manometric a-LES. The damaged LES is distal to the end of the residual LES at manometry and therefore identical in its pressure characteristics to the proximal stomach.

In a patient with LES damage, the distal limit of the manometric LES is *not* the end of the esophagus (Fig. 1.2). The true end of the esophagus includes the damaged a-LES. Any manometric interpretation that makes the assumption that the esophagus ends at the distal end of the manometric LES is potentially wrong by as much as 35 mm (the entire initial a-LES length). For example, if the distal limit of the manometric LES is above the diaphragmatic pressure impression, this is not necessarily a hiatal hernia because the true end of the esophagus cannot be defined by manometry.

At present, the above formula that defines the LES cannot be applied because two elements, LES damage and the initial LES length, are unknown. As a result, manometry has no practical value in the diagnosis of GERD. However, it illustrates the critically important and misunderstood concept that the manometric definition of the distal end of the a-LES is not the end of the esophagus. The true end of the esophagus must include the damaged a-LES that is present distal to the manometric end of the LES in virtually all people This cannot be measured at present.

In Zaninotto et al. [13], therefore, the measured manometric a-LES does not necessarily represent individual variation of the length of the normal a-LES simply because the subjects had no symptoms of GERD. It could be the result of shortening of the a-LES by progressive a-LES damage. The data in the study can be explained by assuming that the initial a-LES length was 35 mm (the highest length) in all patients, and the distribution represents different degrees of a-LES damage. For example, an asymptomatic person with a measured manometric a-LES length of 22 mm (the median a-LES length in the study) could have an initial length of 35 mm

with 13 mm of a-LES damage (Table 1.1). That person is asymptomatic because the LES, though damaged, is still sufficiently competent to prevent reflux.

The distribution of acid exposure in these volunteers in Zaninotto et al. [13], showed a pH < 4 for a mean of 1.57%, a median of 1.1%, and a range of 0–6% of the 24-h period. This shows that these asymptomatic persons had evidence of mild reflux with 5% reaching the pH test definition for abnormal reflux. This was objective evidence of LES failure despite the fact that they did not have symptoms.

The data in Zaninotto et al. [13], raises the intriguing but obvious probability that the LES has a reserve capacity. It can shorten significantly from its initial length while remaining competent, i.e., there is a phase of compensated LES damage where patients have LES damage within its reserve capacity without significant LES failure and reflux into the thoracic esophagus. A person without significant reflux into the thoracic esophagus will be at zero risk for developing vCLE.

Based on this understanding, we can divide the severity of LES damage into (a) compensated, i.e., LES damage is such that it does not produce LES failure, i.e., the pH test is 0 (green zone in Table 1.1); (b) LES damage that causes infrequent LES failure and mild reflux, i.e., pH test is >0 but pH test normal (<4.5% of time pH < 4 or DeMeester score < 14) vCLE is extremely unlikely in such patients (orange zone in Table 1.1); and (c) severe LES damage with LES failure sufficient to produce an abnormal pH test and a high prevalence of vCLE (red zone in Table 1.1).

This further refines our objective into an LES-based objective to prevent vCLE: *prevention of a-LES damage beyond the point where reflux is sufficiently severe to cause vCLE.* In Table 1.1, this corresponds to preventing a-LES damage from reaching 25 mm. When there is a measure of a-LES damage, there is a range of 0–25 mm of LES damage that is available for intervention to prevent progression of LES damage. Prevention of vCLE becomes theoretically very feasible in this method.

This new objective clearly shows the futility of present management of GERD. The presently accepted criteria that define GERD (troublesome symptoms, erosive esophagitis, an abnormal pH test, and a defective LES on manometry where the a-LES is <10 mm) are the very things that must be prevented if we hope to prevent esophageal adenocarcinoma.

1.5.2 Result of a-LES Damage: the Dilated Distal Esophagus

A largely unappreciated normal function of the a-LES is to maintain the tubular shape of the abdominal esophagus. The high resting pressure of the a-LES continually opposes the dilatory tendency of the positive (around +5 mmHg) intraluminal pressure of the abdominal esophagus.

When the a-LES is damaged, the protection provided by the tonic contraction of the LES is lost. The dilatory positive intraluminal pressure will be accentuated during meals when the stomach distends and the intragastric pressure increases. The distal abdominal esophagus that has lost LES pressure will therefore dilate to form the dilated distal esophagus [14] (Fig. 1.3).

With LES damage, the tubular abdominal esophagus shortens the damaged esophagus dilates [15], takes up the gastric contour, becomes part of the reservoir, and the angle of His becomes more obtuse [16]. Mucosal rugal folds, which are a feature of all reservoir organs, develop in this dilated distal esophagus that results from loss of abdominal LES function (see below).

The dilated distal esophagus has a variable length that is equal to the amount of shortening of the a-LES due to damage. The equation that defines the a-LES now resolves as follows:

$$\begin{aligned}&\text{Initial length of a} - \text{LES}\\&= \text{length of residual a} - \text{LES}\left(\text{tubular abdominal esophagus}\right)\\&+\text{length of LES damage}\left(\text{dilated distal esophagus}\right)\end{aligned}$$

The end of the tubular esophagus, which has been used by pathologists to define the GEJ since Hayward in 1961 [17], is proximal to the true GEJ by the length of the dilated distal esophagus.

This "gastricization" of the abdominal esophagus that has lost LES tone occurs at a manometric, endoscopic, and gross anatomic level. This has led to confusion that has created error in this region from the beginning of time and continues to the present [18].

We will show that it is only the correct interpretation of the histology of this region that can resolve this error.

1.5.3 Mechanism of a-LES Damage

LES damage is the result of pressure exerted from below as a result of a heavy meal that causes gastric overdistension. Ayazi et al. [19], and Robertson et al. [20], showed elegantly that gastric overdistension causes "effacement" of the distal part of the LES, resulting in a temporary decrease in LES length. The squamous epithelium lining the effaced LES is exposed to gastric juice because the pH transition point has moved proximally (Fig. 1.4).

The phenomenon of effacement of the distal end of the LES can be demonstrated at endoscopy. In a person with normal endoscopy, the SCJ is the gastroesophageal junction (GEJ). In retroflex view, when the stomach is insufflated with air, the SCJ moves downward and becomes visible. When the same thing happens during a heavy meal, the squamous epithelium is in the stomach, below the pH transition point.

There is a pocket of strong acid at the height of the food column during a meal [21]. Repeated and frequent exposure of the squamous epithelium to this acid pocket during gastric overdistension during heavy meals results first in reversible injury to the distal esophageal squamous epithelium followed by permanent columnar metaplasia of the squamous epithelium.

If LES damage occurs because of pressure from below, it must follow that LES damage begins at its distal end and progresses upward. Loss of length therefore begins in the distal a-LES. Robertson et al. [20], showed that early LES shortening produced by a heavy meal in asymptomatic volunteers was entirely in the abdominal segment and did not affect the thoracic LES.

LES damage can therefore be considered to be basically the result of an eating disorder. Viewed in this light, each person can be regarded as having a unique relationship between his/her eating habit, the response of the LES to this overeating, and the damage caused to the esophageal squamous epithelium by exposure to gastric juice.

At one extreme, the patient's LES is not damaged by the effect of his/her eating habit. This patient never has LES failure and reflux; the pH test is 0; this person never gets GERD. At the other extreme, the patient's LES is damaged early in life by an excessive eating habit and/or an LES susceptible to damage and progresses rapidly to LES incompetence and severe reflux into the thoracic esophagus at a relatively young age. This damage includes erosive esophagitis and becomes irreversible when vCLE occurs.

Between these two extremes is the entire clinicopathologic spectrum of GERD. Progression of GERD can therefore be defined by the rate of progression of LES damage resulting from a person's eating habit (Table 1.2).

Table 1.2 Changes with age of the functional residual length of the abdominal LES assuming that the original length at maturity is 35 mm that LES damage begins at age 15 years and that LES damage has a linear progression over the long term

Rate of LES damage	At 25 years	At 35 years	At 45 years	At 5 5 years	At 65 years	At 75 years
1 mm/decade	34 mm	33 mm	32 mm	31 mm	30 mm	29 mm
2 mm/decade	33 mm	31 mm	29 mm	27 mm	25 mm	23 mm
3 mm/decade	32 mm	29 mm	26 mm	23 mm	20 mm	17 mm
4 mm/decade	31 mm	27 mm	23 mm	19 mm	15 mm	11 mm
5 mm/decade	30 mm	25 mm	20 mm	15 mm	10 mm	**5 mm**
6 mm/decade	29 mm	23 mm	17 mm	11 mm	**5 mm**	**0 mm**
7 mm/decade	28 mm	21 mm	14 mm	**7 mm**	**0 mm**	**0 mm**
8 mm/decade	27 mm	19 mm	11 mm	**3 mm**	**0 mm**	**0 mm**
9 mm/decade	26 mm	17 mm	**8 mm**	**0 mm**	**0 mm**	**0 mm**
10 mm/decade	25 mm	15 mm	**5 mm**	**0 mm**	**0 mm**	**0 mm**

NOTE: The abdominal LES lengths in green represent lengths at which the LES is likely to be competent. The length in orange represent an LES that is susceptible to failure with gastric distension (i.e. at risk of post-prandial reflux). The lengths in red represent an LES that is below the length at which LES failure occurs at rest.

NOTE: The abdominal LES lengths in green represent lengths at which the LES is likely to be competent. The lengths in orange represent an LES that is susceptible to failure with gastric distension (i.e., at risk of postprandial reflux). The lengths in red represent an LES that is below the length at which LES failure occurs at rest

1.5.4 Relationship Between a-LES Length and LES Failure

LES damage is a progressive phenomenon. When looked at from the perspective of LES damage, progression is inexorable from the onset of LES damage to the end point defined as the end of life, or some intervention that stops the progression such as an anti-reflux procedure.

PPI therapy has no positive impact on the rate of progression of LES damage. By removing the pain associated with reflux and allowing the patient to eat excessively, PPIs may actually prevent the body's natural defense against progression of LES damage.

In general, the greater the LES damage, the greater is the severity of reflux. Kahrilas et al. [22], demonstrated beautifully the close relationship between decreasing LES length and LES failure. They measured baseline total LES length in three groups with increasing severity of GERD: patients who had no symptoms of GERD ("normal"), patients with GERD without a hiatal hernia, and patients with GERD who had a hiatal hernia.

The baseline LES length in the fasting state was progressively less in normal persons compared to non-hernia GERD to hernia-GERD. This correlated with an increase in baseline reflux as measured by a pH electrode placed 5 cm above the upper border of the LES.

In this study, Kahrilas et al. [22], infused air into the stomach at 15 ml/min, causing progressive gastric distension. This caused an additional shortening of the LES of 5–7 mm from baseline in all three groups as distension increased. The additional temporary shortening of the LES was similar in the three groups, suggesting that gastric overdistension caused LES exposure to gastric contents in a linear manner. During the temporary shortening of the LES with gastric distension, the number of reflux episodes and total acid exposure in the esophagus increased significantly and most prominently in the hernia-GERD group. This showed that a damaged LES with a shorter baseline length was more susceptible to failure when exposed to gastric distension.

This study confirms that a-LES length is a critical determinant of the severity of reflux (objectively measured in a pH test). It also shows that significant reflux can occur during the postprandial phase in asymptomatic persons.

1.6 Histologic Measurement of a-LES Damage

The objective of preventing vCLE is not possible at the present time because there is no test that has the ability to predict with sufficient accuracy in those patients at high risk of progressing to vCLE. The use of symptom severity has no value; some patients with vCLE are asymptomatic. The control of symptoms with PPIs has a negative correlation with prevalence of vCLE [10]. There is no defined value in the pH test or manometry that can predict impending or future vCLE. The presence of severe erosive esophagitis and intestinal metaplasia in a biopsy of the SCJ in the endoscopically normal GERD patient has a 20–25% known progression to vCLE within 5 years, but this has not led to a recommendation to intervene in some way to prevent vCLE.

We propose a new method of achieving the ability to predict high risk of impending and future vCLE. This is the measurement of the dilated distal esophagus by histology. We will show that the length of the dilated distal esophagus is equal to the

length of metaplastic columnar epithelium that is found *distal* to the endoscopic GEJ [14]. In turn, this is equal to the shortening by damage of the a-LES.

This provides, for the first time, a method of measuring a-LES damage, the cause of GERD. This is of such fundamental value to the understanding of GERD that it has the potential to transform the management of GERD.

At the present time, two false dogmas prevent the application of this new method of diagnostic testing. These are: (a) the false dogma that cardiac epithelium is a normal proximal gastric epithelium and (b) that the proximal limit of rugal folds and/or the distal limit of the tubular esophagus define the GEJ. The result of these two false dogmas is that the entire pathology of LES damage is mistaken as "normal proximal stomach." The failure of understanding at such a fundamental level explains the present chaos in the diagnosis and management of GERD with its disastrous patient outcomes of refractory GERD and adenocarcinoma.

1.6.1 Definition of Normal Histology of the Esophagus and Stomach

It is remarkable that GERD, a disease that results from damage to esophageal epithelium by gastric acid, has no histopathologic criteria that have practical value in present diagnosis. Before we accept the fact that histology does not play a role in the diagnosis of early GERD, it is important to ask the right questions: *Is there any possibility that we are overlooking some histologic change that is diagnostic of GERD? Are we looking in the right places? Is there any possibility of error in our definitions? Could we be calling the distal esophagus damaged by GERD the proximal stomach? Is it possible that we are so wrong?* The simple answer to all these questions is a vehement "yes."

To begin to answer these questions and explore histologic criteria for defining early GERD, it is important to first define the epithelial types seen in the esophagus and stomach [23]. There are only three basic epithelial types that occur from the proximal end of the esophagus to the pyloric antrum [23, 24]. These are: (a) stratified squamous epithelium, this is limited to the esophagus in the human and is *always* present; (b) gastric oxyntic mucosa, this is limited to the proximal stomach and not found in the esophagus and is *always* present (Fig. 1.5); (c) metaplastic

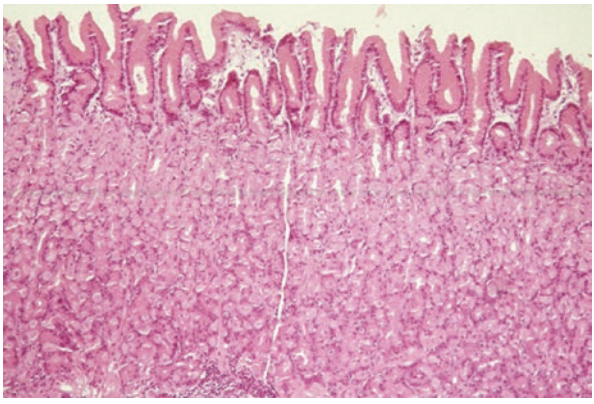


Fig. 1.5 Normal gastric oxyntic epithelium. This shows a surface layer and short foveolar pit composed of mucous cells and a long, straight tubular gland that contains parietal and chief cells. No mucous cells are seen below the foveolar pit. Hematoxylin and eosin stain

columnar epithelia, these are *always* derived from chronic exposure of esophageal squamous epithelium to gastric juice but are *not always* present. When present, however, they are *always* interposed between the distal limit of esophageal squamous epithelium and the proximal limit of gastric oxyntic epithelium (Fig. 1.6).

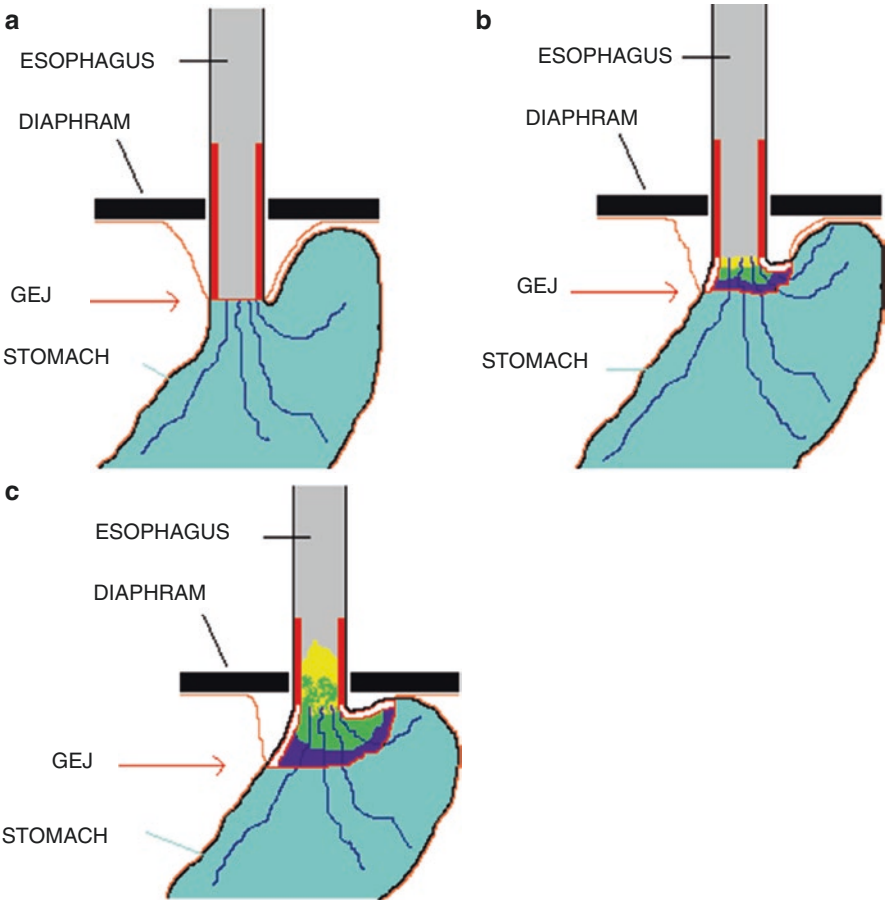


Fig. 1.6 Progression of the gap between the squamocolumnar junction and gastric oxyntic epithelium with increasing severity of GERD. (**a**) Normal state with no gap; the squamous epithelium (gray) transitions directly to gastric oxyntic epithelium (blue); note rugal folds (lines). (**b**) Metaplastic columnar epithelium limited to the dilated distal esophagus. This is depicted with intestinal metaplasia (yellow), cardiac epithelium (green), and oxyntocardiac epithelium (purple). Note that these epithelia have replaced squamous epithelium. The proximal limit of gastric oxyntic epithelium has not moved. The area of columnar metaplasia of squamous epithelium is dilated and has developed rugal folds. This is the dilated distal esophagus resulting from abdominal LES damage. This is presently mistaken for proximal stomach (gastric cardia) because it is distal to the end of the tubular esophagus and the proximal limit of rugal folds; (**c**) Final phase of progression where LES damage has led to sufficient reflux into the esophageal body to cause vCLE. NOTE: The damaged LES is shown as a white wall that has replaced the red wall where the LES is intact

Metaplastic columnar epithelium is cardiac epithelium. Cardiac epithelium *never* occurs normally in the proximal stomach. It consists of three histologic variants (Fig. 1.7): (a) pure cardiac epithelium composed of only mucous cells; (b) cardiac epithelium with parietal cells admixed with mucous cells in the glands (oxyntocardiac epithelium); and (c) cardiac epithelium with goblet cells, which define intestinal metaplasia. The prevalence of these three columnar epithelial types is variable. Intestinal epithelium is the least common and oxyntocardiac epithelium the most prevalent.

The four columnar epithelial types (i.e., three metaplastic and gastric oxyntic epithelium) can be precisely defined by simple histologic criteria based on the presence or absence of mucous cells, parietal cells, and goblet cells (Table 1.3).

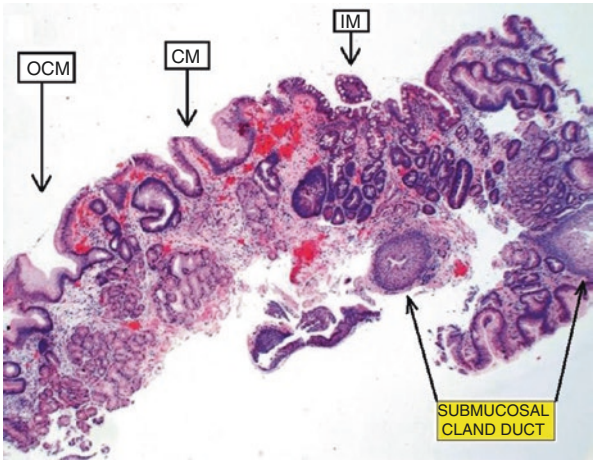


Fig. 1.7 The histologic composition of the dilated distal esophagus, showing the three metaplastic columnar epithelial types. Intestinal metaplasia with goblet cells (IM) is proximal, cardiac epithelium (CM) is in the middle, and oxyntocardiac epithelium with parietal cells (OCM) is distal (on the left). Note the presence of submucosal gland ducts. Ducts of submucosal glands are specific for the esophagus; their presence proves that the location of this tissue is esophageal

Table 1.3 Histologic criteria for diagnosis of four different columnar epithelial types that are encountered in the esophagus and proximal stomach

	Mucous cells in glands[a]	Parietal cells	Goblet cells
Gastric oxyntic epithelium	–	+	–[b]
Cardiac epithelium	+	–	–
Oxyntocardiac epithelium	+	+	–
Intestinal epithelium	+	–	+

Gastric oxyntic epithelium lined the entire proximal stomach. Cardiac, oxyntocardiac, and intestinal epithelia are, when present, interposed between the squamous epithelium and gastric oxyntic epithelium (i.e., form the squamo-oxyntic gap)

Note: There is no epithelium defined in this scheme that has both parietal and goblet cells in one foveolar-gland complex. This is an extremely rare finding; when found, goblet cells take precedence and the epithelium is designated as intestinal

aMucous cells are present at the surface and foveolar pit in all epithelial types; it is the presence of mucous cells in glands below the foveolar pit that are relevant to the definitions

bGastric oxyntic epithelium with atrophic gastritis can have goblet cells. This is intestinal metaplasia in gastric oxyntic epithelium, which is different than cardiac (metaplastic esophageal) epithelium with intestinal metaplasia

The definition of the epithelial type is applied to every unit of the epithelium, which is defined as a single foveolar-gland complex. Multiple epithelial types can therefore be present in a small area (Fig. 1.7).

The diagnosis of these four epithelial types has high precision with minimal requirement for training and experience, and it is easy. More important than training is a belief in the pathologist that differentiating between these epithelial types has value. Careful study of routine sections stained by hematoxylin and eosin is adequate for accurate diagnosis.

The extent of cardiac epithelium (with and without parietal and/or goblet cells) between the endoscopic GEJ (proximal limit of rugal folds and/or end of tubular esophagus) defines the length of the dilated distal esophagus and is therefore a measure of a-LES damage. This can be measured with a high level of accuracy with an appropriate tissue sample.

1.6.2 Definition of the GEJ

From an anatomical standpoint, it is very important to have a precise and accurate definition of the gastroesophageal junction (GEJ). The most widely used definition of the GEJ is the proximal limit of rugal folds [2, 25]. This is a reasonably precise endoscopic landmark and can usually be seen in gross specimens. However, there is absolutely no evidence that it accurately represents the GEJ. The basis of the definition is the opinion of experts [2, 26]. For an opinion-based definition, for which evidence is lacking, this definition of the GEJ has incredible universal acceptance.

Chandrasoma et al. [27], has shown conclusively that this endoscopic definition of the GEJ is incorrect (Fig. 1.8a, b). They showed that the area distal to the endoscopic GEJ lined by cardiac epithelium (with and without parietal and/or goblet cells) was esophagus by virtue that submucosal glands that are specific to the esophagus were present in and concordant with the length of the dilated distal esophagus (Fig. 1.9).

The correct definition of the true GEJ is the proximal limit of gastric oxyntic epithelium. This never changes its position. In the person with LES damage, whether symptoms of GERD are present or not, the true GEJ is separated from the endoscopic GEJ by cardiac epithelium (with and without parietal and/or goblet cells; Fig. 1.6).

The present use of the endoscopic GEJ results in an error that is equal to the length of the dilated distal esophagus. Ironically, the greater the amount of LES damage (i.e., the more severe the GERD), the greater the error. This error is made at endoscopy, manometry, and gross pathology. It is also made at histology by pathologists who believe that cardiac epithelium is part of the normal stomach. Only pathologists who understand that cardiac epithelium is always an abnormal metaplastic esophageal epithelium have the key to the truth.

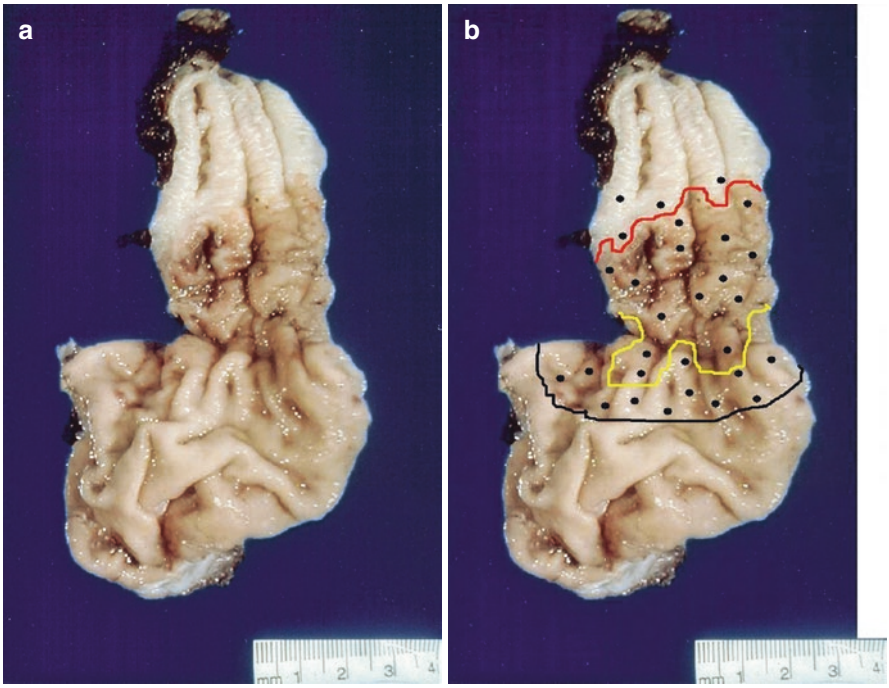


Fig. 1.8 Present incorrect and correct interpretation of an esophagectomy specimen. (**a**) This specimen shows a tubular esophagus lined by 5.5 cm of vCLE above the proximal limit of rugal folds. There is an ulcerated adenocarcinoma immediately distal to the SCJ. The area distal to the end of the tubular esophagus is lined by rugal folds. This area will be interpreted as proximal stomach by present criteria for defining the GEJ at endoscopy and gross dissection. (**b**) Histologic findings show that 20.5 mm of the area distal to the end of the tubular esophagus and containing rugal folds is lined by cardiac epithelium with intestinal metaplasia proximally and oxyntocardiac epithelium distally. The red line is the SCJ; the yellow line is the distal limit of intestinal metaplasia; the black line is the proximal limit of gastric oxyntic epithelium which is the true GEJ. The dilated distal esophagus between the end of the tubular esophagus and the true GEJ contains submucosal glands (black dots) whose extent is concordant with the length of cardiac epithelium (with parietal and goblet cells). This is proof of the dilated distal esophagus

1.6.3 Measurement of the Length of the Dilated Distal Esophagus

The dilated distal esophagus can be precisely measured by examining the mucosa distal to the endoscopic GEJ. This can be done at autopsy and in resected specimens by taking a vertical section with its proximal end at the SCJ (in a person without vCLE) extending distally till the proximal limit of gastric oxyntic epithelium is reached (30 mm beyond the SCJ to ensure that gastric oxyntic epithelium is reached) [27, 28]. When vCLE is present, the dilated distal esophagus is measured from the endoscopic GEJ (end of tubular esophagus or proximal limit of rugal folds) to the proximal limit of gastric oxyntic epithelium (Fig. 1.8).

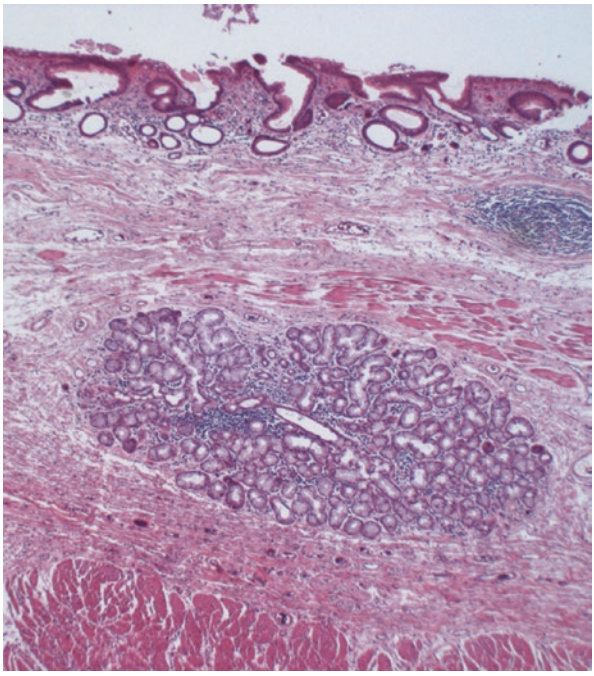


Fig. 1.9 Full thickness section of dilated distal esophagus showing cardiac epithelium with an underlying submucosal gland

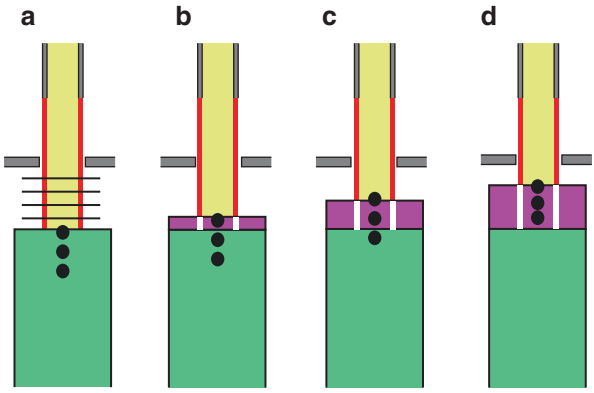


Fig. 1.10 Multilevel biopsy protocol to assess the length of the dilated distal esophagus. Three biopsies are taken distal to the SCJ at 5 mm intervals. Yellow = squamous epithelium; green = gastric oxyntic epithelium; purple = metaplastic columnar epithelium in the dilated distal esophagus; orange line in wall of esophagus = functional LES; and white = damaged LES. Patient A: zero dilated distal esophagus = 0 a-LES damage; Patient B: 5 mm dilated distal esophagus/a-LES damage; Patient C: 10 mm dilated distal esophagus/a-LES damage; Patient D: 15 mm dilated distal esophagus/a = LES shortening

The length of the dilated distal esophagus can be assessed at endoscopy by measured biopsies taken at 5 mm intervals from the SCJ, extending distally to a point 30 mm distal to the SCJ (Fig. 1.10). It is unlikely that this labor-intensive, endoscopist-dependent, and cumbersome multilevel biopsy protocol will be

acceptable or accurate. The inability to orient each biopsy will result in an error in the measurement of at least 1–2 mm. Ideally, a new biopsy instrument should be developed that can obtain a single, intact 25 mm, vertical biopsy of the mucosa. This will provide a measurement that has a level of accuracy with a micrometer and identical to a vertical section taken from a resection specimen.

1.6.4 Variation in the Length of the Dilated Distal Esophagus

The reported length of the dilated distal esophagus varies in published reports from 0 to 28 mm in patients without vCLE. Its theoretical length is the initial length of the a-LES, which is 35 mm. When the entire a-LES has been destroyed, the angle of His essentially disappears and hiatal hernia occurs.

Normally, in a person with a completely intact LES, there is no dilated distal esophagus. The entire abdominal esophagus is tubular, lined by squamous epithelium to its end (the GEJ) where it transitions to gastric oxyntic epithelium. There is no metaplastic columnar epithelium (i.e., cardiac epithelium). Chandrasoma et al. [24], and other groups [29], have illustrated a SCJ with a direct transition of squamous to gastric oxyntic epithelium without cardiac epithelium (Fig. 1.11a, b).

The abnormal state where the LES is damaged is defined by the presence of a dilated distal esophagus. The length of the dilated distal esophagus, as measured by histology, has a strong correlation with the cellular changes associated with GERD.

Chandrasoma et al. [24], reported a length of 0 to 8.05 mm in persons without symptoms of GERD at autopsy (Fig. 1.12). Kilgore et al. [30], in a study of 30 pediatric autopsies confirmed that cardiac epithelium measured a maximum of 4 mm.

Robertson et al. [20], in a study of asymptomatic volunteers, reported that the length of cardiac epithelium was a median of 2.50 mm in persons with central obesity, significantly greater than the 1.75 mm in those without obesity. The patients with central obesity also had a shorter a-LES.

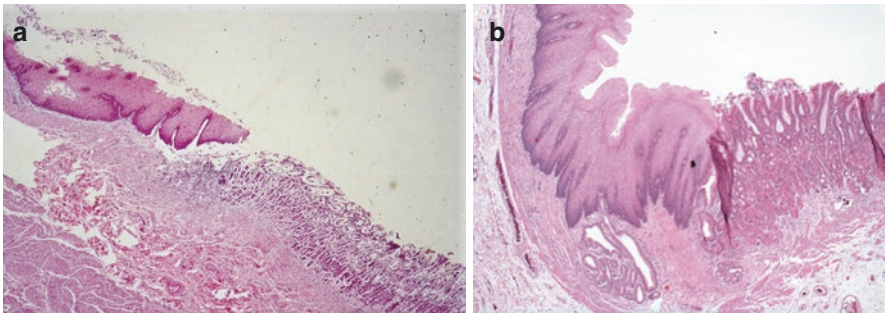


Fig. 1.11 (**a**) A section across the SCJ at autopsy showing direct transition of squamous epithelium to gastric oxyntic epithelium, characterized by the typical straight tubular glands containing only parietal and chief cells below the foveolar pit. (**b**) A zero squamo-oxyntic gap in a 77-year-old male undergoing esophagectomy for squamous carcinoma. There is a small mucous gland with a duct exactly at the end of the esophagus

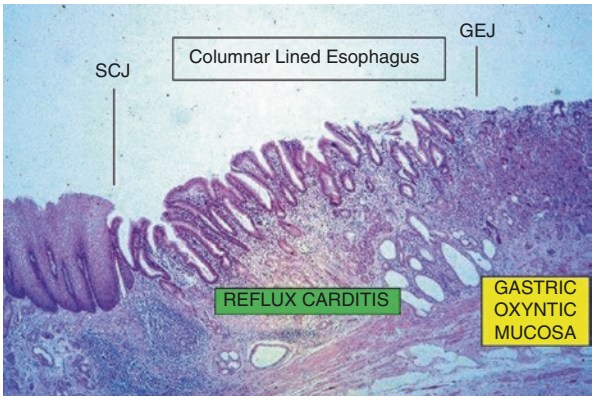


Fig. 1.12 The histologic gap composed of cardiac and oxyntocardiac epithelia between the distal end of the squamous epithelium and proximal limit of gastric oxyntic epithelium. This is 2 mm long in this section. This is the histologic definition of the dilated distal esophagus. This patient has 2 mm of a-LES damage

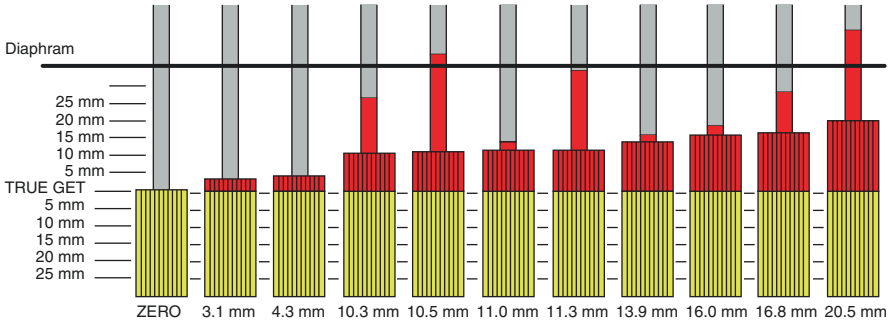


Fig. 1.13 Esophagectomy specimens in 10 patients, 2 patients with squamous carcinoma and 8 with adenocarcinoma arising in Barrett esophagus. The normal state is shown on the extreme left. The dilated distal esophagus measures 3.1 and 4.3 mm in the two patients with squamous carcinoma and 10.3–20.5 mm in the 8 patients with adenocarcinoma. Blue = intestinal metaplasia; Red = cardiac epithelium; Black = oxyntocardiac epithelium; Yellow = gastric oxyntic epithelium; black vertical lines indicate rugal folds

The dilated distal esophagus is longer in patients with GERD and correlates with the severity of GERD. In the only study with multilevel biopsies in a population of GERD patients, Ringhofer et al. [31], reported the findings at the endoscopic GEJ and on both sides of it at intervals of 0.5 cm. Cardiac epithelium (with and without parietal and/or goblet cells) was found in 100% at the GEJ, in 81% in the biopsy taken 5 mm distal to the GEJ, and in 28% in the biopsy taken10 mm distal to the GEJ.

Chandrasoma et al. [27], reported the findings in ten esophagectomy specimens that had a sharp transition from the tube to the sac at the exact location of well-defined proximal rugal folds. Eight patients had adenocarcinoma of the esophagus secondary to Barrett esophagus; in these patients, the dilated distal esophagus measured 10.3–20.5 mm (Fig. 1.13). In two patients, who had squamous carcinoma without vCLE, the dilated distal esophagus measured 3.1 and 4.3 mm (Fig. 1.13). Sarbia et al. [28], in a similar study of esophagectomy specimens in 36 patients with squamous carcinoma showed that cardiac epithelium (with and without parietal

and/or goblet cells) was present distal to the end of the tubular esophagus to a length that varied from a minimum of 4 mm (median) to a maximum length of 11 mm (median). In eight (25%) patients, cardiac and/or oxyntocardiac epithelium was situated over submucosal glands.

The true GEJ cannot be seen at endoscopy because the dilated distal esophagus and proximal stomach both have rugal folds. With standard endoscopy, it is not possible to differentiate cardiac and gastric oxyntic epithelium. It is, however, possible that newer endoscopic modalities, such as confocal microscopy and optical coherence tomography, can do this. At present, though, only histologic examination is capable of identifying the true GEJ.

1.7 A New Pathologic Test of LES Damage

We have proposed a new test that can accurately measure the presence and severity of a-LES damage in any person, whether or not there are symptoms of GERD. LES damage is equal to the measured length of the dilated distal esophagus. This is the length of cardiac epithelium (with and without parietal and/or goblet cells) between the SCJ and the proximal limit of gastric oxyntic epithelium in persons without a vCLE at endoscopy.

With a suitable specimen, this can be measured with an accuracy within 1 μm. The measurement is made on a standard histologic slide with a standard microscope that has an ocular micrometer. These are available in every pathology laboratory the world over. The test is inexpensive.

1.7.1 Classification of GERD by the Results of the New Test

The ability to measure a-LES damage opens a new dimension in the diagnosis of management of GERD. The entire spectrum of the disease from the normal state to the most severe disease can be understood by the extent of damage to the 35 mm of the a-LES (Table 1.1). Correlations between severity of a-LES damage and frequency of LES failure, severity of reflux, and severity of cellular changes in the esophagus are likely to be more accurate than with any other measure.

Theoretically, we can divide GERD into four stages based on the amount of a-LES damage. To do this, we will make the following assumptions: (a) the initial length of the a-LES is 35 mm; (b) LES failure correlates with a functional a-LES length of <10 mm; (c) a-LES damage has a linear progression with a variable rate in any person; and (d) dynamic shortening of the a-LES with a meal has a maximum of 10 mm.

Four stages of GERD emerge in this new method:

1. *Normal:* There is no LES damage. The residual a-LES length is 35 mm. Defined by the absence of a dilated distal esophagus. This is rare in adults. However, I have encountered 67 male patients without cardiac epithelium in an esophagectomy done for squamous carcinoma.

2. *The phase of compensated a-LES damage*: There is a-LES damage <15 mm defined by a dilated distal esophagus of <15 mm. Residual a-LES length is >20 mm. This is the finding in 70% of the population at large who do not have symptoms of GERD. Their LES is competent at all times and there is no significant reflux on a pH test (zero to well below normal).
3. *Mild GERD*: There is a-LES damage of 15–25 mm, defined by a dilated distal esophagus of 15–25 mm. Residual a-LES length is 10–20 mm. This is the finding in the 70% of patients with GERD. Their symptoms are controlled with PPIs and there is a low prevalence of vCLE. Their LES tends to fail during the postprandial period when dynamic shortening decreases the a-LES length to <10 mm. At the low end of this range, the patients are at the onset of disease with infrequent postprandial reflux. At the high end, they are at the cusp of severe GERD. Somewhere in the higher end of this range, they may develop vCLE. They have significant reflux with a high normal or abnormal pH test.
4. *Severe GERD*. There is a-LES damage of >25 mm. The residual a-LES in the fasting state is below the threshold at which LES failure occurs. Reflux is severe and unrelated to meals. There is a high prevalence of refractory GERD and vCLE.

1.7.2 Evidence Base Supporting the New Diagnostic Method

We have presented the data that show strong support that the length of the dilated distal esophagus, measured by the length of cardiac epithelium (with and without parietal and/or goblet cells) between the endoscopic GEJ and proximal limit of gastric oxyntic epithelium, accurately represents LES damage. We have shown that the length of a-LES damage can be measured accurately within 1 μm in autopsy and resected specimens.

Unfortunately, there is almost no data relating to the measured a-LES damage in either asymptomatic people or patients with GERD. This is the result of the erroneous beliefs that cardiac epithelium lines the normal proximal stomach and the GEJ is defined by the proximal limit of rugal folds. These false dogmas have resulted in a general recommendation by all gastroenterology societies that biopsies should not be taken in the person who is endoscopically normal and has inhibited data being accumulated [2, 8]. As a result, there has never been a systematic study of the dilated distal esophagus.

We have made several assumptions in using the new test to classify patients into four stages based of a-LES damage. These assumptions are based on a careful examination of the best available evidence. However, the evidence base is scanty. There is an opportunity to study the dilated distal esophagus at every upper endoscopy. Our hope is that knowledge of this new diagnostic test will stimulate esophagologists to produce data that will refine the criteria for defining these various stages of GERD.

1.7.3 Prediction of Progression of LES Damage

LES damage is irreversible. There is evidence that a-LES damage progresses in an inexorably relentless manner. Progression is not impacted in any way by medical therapy. The cause of LES damage is an eating disorder that can be described as

LES-unfriendly. Once this eating habit is established, the rate of progression of a-LES damage is likely to be linear over the long term.

The new test of a-LES damage provides a unique ability to predict the status of the a-LES in the future, if it is assumed that progression of LES damage is linear over the long term. Theoretically, if a-LES damage is measured on two occasions separated by a significant interval, a simple straight-line slope can be drawn that extrapolates the extent of damage back into the past and forward into the future.

The prediction is also possible with one measurement with the assumption that a-LES damage begins at an early age, say 15 years old, when a person's adult eating habit is established. There are now two points that permit the slope of future a-LES damage to be drawn.

The ability to predict future a-LES damage permits the identification of persons that are at risk of progressing to severe GERD defined by vCLE in the future long before the point at which the person is in danger. This permits intervention to slow the progression of LES damage. If a successful intervention can be developed, progression to severe GERD and vCLE can be prevented. *The objective of preventing vCLE is achieved. Adenocarcinoma will not occur without vCLE.*

1.8 Potential Value of the New Test in the Management of GERD

The new test has obvious value in the management of GERD.

1.8.1 Exclusion of GERD as a Cause of Symptoms

At the present time, there is no diagnostic test that can accurately determine whether symptoms that could possibly be caused by GERD are actually caused by GERD. Diagnosis commonly depends on an empiric PPI test that is known to have a significant false positive rate [2]. The consequence of a false positive empiric PPI test is that many people are unnecessarily placed on long-term PPI therapy who do not have GERD. The new test provides a definitive answer: *if the measured a-LES damage is < 15 mm (or a number based on new data), the symptoms are not caused by GERD.*

1.8.2 Stratification of GERD Treatment According to Risk

At the present time, all GERD patients are treated with a one-size-fits-all regimen of acid-reducing drugs as needed to control symptoms. The ability of the new test to identify the minority of people who are at risk to progress to vCLE allows a concentrated attack on this group. The interval between the test and the predicted time of occurrence of a-LES damage sufficient to cause vCLE is likely to be many decades. This allows time to watch the patient, repeat testing to verify findings, try a test of dietary control, and intervene to prevent progression of LES damage before vCLE develops.

1.9 What Needs to Happen for the New Test to Work

Like any new scientific test, there is much research, development, and testing that needs to be done to bring the test to fruition. We can conceive some of these at this time. However, when the test is recognized as being valuable, novel developments, yet not conceived, are likely to emerge.

1.9.1 The Need to Remove Errors in Interpretation

The evidence base that cardiac epithelium is always a metaplastic esophageal epithelium is powerful. The present dogma that cardiac epithelium is the normal lining of the proximal stomach must be eliminated.

The evidence that the true GEJ is the proximal limit of gastric oxyntic epithelium and cannot be seen at endoscopy is powerful. The opinion-based definitions that are universally used to define the GEJ at endoscopy and gross dissection (proximal limit or rugal folds and end of the tubular esophagus) must be eliminated.

1.9.2 The Need for a New Biopsy Device

Accurate measurement of the dilated distal esophagus is not possible with present biopsy forceps. A critical length of between 15 and 25 mm of a-LES damage differentiates mild GERD at its onset to severe GERD. Accuracy is vital. With present biopsy forceps, multiple-level biopsies distal to the endoscopic GEJ need to be performed. These are likely to be extremely difficult and time consuming and therefore fraught with error. A simple new biopsy device that can remove a piece of mucosa measuring 25 mm long, 2 mm wide, and 1 mm deep should be easy to produce. This will provide a mucosal biopsy sample that is equivalent to a section taken from a resected specimen that we know can produce a measurement of the dilated distal esophagus that is accurate to within 1 μm.

1.9.3 The Need for Data on Asymptomatic Persons and GERD Patients

A large database is the essential requirement for defining criteria for length of a-LES damage that is associated with vCLE. This is the critical value because preventing vCLE is the objective and basis of preventing adenocarcinoma. We have used the best available evidence at this time to suggest that >25 mm of a-LES damage is the earliest point at which vCLE occurs. This may be optimistic; it is possible that this number is closer to 20 mm. The important thing is that examination of a sufficient number of people *will* provide that number.

1.9.4 Non-endoscopic Measurement of a-LES Damage

At present, all biopsy methods are designed for use with an endoscope. The need for endoscopy to perform the new test will seriously limit its usage. Endoscopy will have low value in the assessment of GERD if the new test becomes a stand-alone diagnostic test. In that event, it will be important to develop non-endoscopic methods of inserting the biopsy device to the appropriate location and orientation to allow the required biopsy to be taken. If such a method can be developed that is safe, quick, cheap with the ability to be done in the doctor's office without the need for sedation, the scope of the test can be expanded dramatically to the general population, allowing screening and early diagnosis.

1.9.5 A New Effective Method or Preventing Progression of a-LES Damage

There are many procedures presently available to repair or augment a defective LES. Some are done by endoscopy and other require laparoscopic surgery. These all have less than perfect and variable effectiveness with significant complications.

The new need is simpler. The objective is not to repair or augment a defective LES. It is to prevent progression of a damaged LES with significant residual function that is predicted to progress to severe damage in the future. This is a far easier surgical problem. It is very likely that many of the techniques that currently have low success rates in augmenting a defective LES will have more success in preventing progression of damage in a partially damaged LES.

1.10 Conclusion: A New Vision for the Future

We envision the management of GERD in the future to be very different with the availability of the new test. At its ultimate end point of development, a biopsy device will be used in a doctor's office as a screening test in the population at around age 30–35 years unless symptoms appear earlier. The test will be simple, cheap, and relatively painless. It will identify those at risk in the future with a timeline that shows the exact status of the a-LES at specific times in the life of the patient. We can equate it to a "Pap smear" for cancer of the uterine cervix.

The patient will have choices depending on the results of the test:

(a) The test predicts that a-LES damage will remain within the reserve capacity indicating that there will be no GERD. The person can be confident that esophageal adenocarcinoma will not occur and no treatment will ever be necessary. The senior author (PC) has had this assessment. He knows that at age 56 years, he had 4 mm of a-LES damage, measured in an endoscopic biopsy of the normal SCJ. Biopsies >5, >10, >15, and >20 mm distal to the SCJ consisted of

normal gastric oxyntic epithelium. By the algorithm that predicts linear progression, he is predicted to have 8 mm of a-LES damage at age 97 years. He will always stay in the green zone of Table 1.1 with LES damage that is within its reserve capacity. He will never develop GERD, Barrett esophagus, or esophageal adenocarcinoma. No one else in the world has that certainty.

(b) The test predicts the occurrence of LES damage that is likely to cause mild GERD during the expected life span that can be easily controlled with acid-reducing therapy without progression to severe GERD, vCLE, or cancer. This person can opt to let GERD arise and be treated with PPIs for the entire lifetime or undergo the procedure to protect the LES and prevent GERD.

(c) The test predicts future severe LES damage with a high risk of refractory GERD, vCLE, and adenocarcinoma. These persons can develop a long-term treatment protocol with repeat testing, dietary control to slow progression of a-LES damage, and timely intervention with a simple procedure well before the predicted time of LES damage sufficient to cause severe GERD and vCLE.

In all scenarios, knowledge of future a-LES damage allows for stratification of treatment according to the risk of future cellular complications of GERD.

We can only guess whether this vision of a world without GERD and esophageal adenocarcinoma will come true. What is important is that this new method provides us with the possibility that there may be a way to this goal. It will change the perspective toward a belief that GERD, Barrett esophagus, and esophageal adenocarcinoma are preventable. This is better than the present nihilistic attitude where we do nothing and simply hope that our patients will not progress to severe GERD that is refractory to therapy and worse, be complicated by adenocarcinoma.

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Esophageal Function Testing for Gastroesophageal Reflux Disease

2

Ivan Kristo, Milena Nikolic, and Sebastian F. Schoppmann

2.1 Introduction

Esophageal function testing (EFT) has revolutionized modern medicine within the last decade. Importantly, the implementation of high-resolution manometry (HRM) and esophageal pressure topography (EPT) facilitated evaluation of patients with symptoms of esophageal motor disorders or gastroesophageal reflux disease (GERD) [1]. Moreover, novel metrics (Table 2.1) were introduced that led to the introduction of an algorithm, namely the Chicago Classification (CC), to define borders of abnormality [2]. After daily clinical use led to some adaptations, CC version 3.0 is currently being used to categorize disorders by a hierarchical approach [3]. Herewith, we highlight the role of EFT for patients presenting with typical or atypical symptoms of GERD and its consequences on tailored surgical strategies.

2.2 Role of EFT in Patients with Typical Symptoms of GERD

GERD is defined by the Montreal consensus as a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications [4]. Therefore, it is not characterized by symptom perception only, but comprises

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_2

Table 2.1 Pressure topographic metrics according to the Chicago Classification version 3.0 [3]

Distal Contractile Integral (DCI) (mmHg × s × cm)	Amplitude × duration × length of the distal esophageal contraction exceeding 20 mmHg from the transition zone to the proximal margin of the lower esophageal sphincter
Distal latency (DL) (s)	Interval between upper esophageal sphincter relaxation and the contractile deceleration point
Contractile deceleration point	Inflection point along the 30 mmHg isobaric contour at which propagation slows, demarcating peristalsis from ampullary emptying
Integrated relaxation pressure (IRP) (mmHg)	Mean of the 4 s of maximal deglutitive relaxation in the 10-s window beginning at upper esophageal sphincter relaxation and referenced to gastric pressure

also end-organ effects and complications like Barrett's esophagus (BE) [5]. Consequently, due to the varying spectrum of phenotypes, involved physicians, mainly gastroenterologist and surgeons, consider every single patient as unique. From a technical surgical perspective, GERD results as a failure of the anti-reflux barrier, consisting of the lower esophageal sphincter (LES), diaphragmatic crura, and phrenoesophageal ligament [6]. Both length of the LES with its intra-abdominal fraction and resting pressure are addressed by means of HRM and may indicate a patient's predisposition for GERD. Lee et al., retrospectively investigated 1307 patients that were referred for symptoms of GERD and observed that esophageal acid exposure on ambulatory reflux testing was independently associated with decreasing LES pressure and intra-abdominal LES length [7]. Additionally, an age increasing effect, pointing out a degradation over time, was also observed.

Unfortunately, even in patients presenting with typical symptoms of GERD, diagnosis based on clinical history, symptom perception, and its response to empiric PPI treatment is more than questionable [8]. Importantly, Dent et al., performed the DIAMOND trial, a single-blind, single-arm study, where diagnosis of GERD was assessed by questionnaire, physicians, and a PPI trial [9]. Interestingly, even in an expert setting sensitivity and specificity for diagnosis of GERD were 67% and 70%, respectively. Moreover, symptom response to a 2-week course of 40 mg of esomeprazole did not chance diagnostic quality.

Therefore, the Lyon consensus advocates a more complex approach in diagnosing GERD [8]. An additional workup with upper gastrointestinal endoscopy and esophageal functioning testing, comprising of esophageal manometry and ambulatory reflux monitoring (pH or impedance-pH), have distinct functions and roles in the diagnoses of GERD [10].

Currently, the diagnosis of GERD is made based on a combination of symptom presentation, response to antisecretory therapy, and objective testing with endoscopy and ambulatory reflux monitoring. In patients with typical GERD symptoms, HRM may reveal structurally defective LES and is additionally used to locate the LES, thus in the correct placement of transnasal pH-impedance probes in patients undergoing ambulatory reflux monitoring [11]. Furthermore, HRM is needed to rule

Fig. 2.1 Bravo™ wireless telemetry capsule for the assessment of gastroesophageal reflux

out major motility disorder such as achalasia, which would present contraindications to surgical anti-reflux therapies [12].

Consistently, ambulatory reflux monitoring represents the gold standard in the diagnosis of GERD [13–15]. Ambulatory reflux monitoring is able to determine the presence of abnormal esophageal acid exposure, reflux frequency and quality, and symptom association with reflux episodes [16]. It is of high value in nonerosive reflux disease (NERD), preoperative management in patients seeking surgical anti-reflux control, in the evaluation of GERD resistant to medical treatment and in conditions where diagnosis of GERD is unclear [17]. The test can be performed in two ways: a telemetry capsule (Fig. 2.1) or through a transnasal catheter lasting for 24 h [18]. Both ways of pH monitoring show excellent sensitivity (77–100%) and specificity (85–100%) in patients with erosive esophagitis [8]. Nevertheless, adding impedance to pH monitoring improves diagnostic yield and allows better symptom analysis than pH metry alone, especially in patients on PPI therapy [19]. The advantage of the telemetry capsule seems to address patient tolerability, especially needed in children, as well as the option to extend the monitoring period to 48 or even to 96 h [20]. Prolongation of the monitoring period allows for testing on and off PPI therapy in selected situations. Ambulatory reflux monitoring is considered as abnormal when the total acid exposure time (pH < 4) exceeds 6% and the total number of reflux episodes in 24 h exceeds the number of 80. Furthermore, advanced grade esophagitis and complications of GERD, such as presence of Barrett's esophagus or peptic stricture, substantiate the diagnosis of GERD.

2.3 Role of EFT in Patients with Dysphagia

Dysphagia is considered an alarm symptom as it can occur in context of GERD but also be present due to an underlying motility disorder, stricture, eosinic esophagitis, or malignancy [21]. Importantly, in patients with dysphagia esophageal HRM studies are crucial to rule out major and minor motor disorders [22]. HRM consists of a series of ten wet swallows that require a recording assembly comprising multiple closely spaced pressure sensors suitable for capturing the entirety of the deglutitive process (Fig. 2.2). This technology has then been further combined with pressure topography plotting (Clouse plots) in order to generate esophageal pressure topography [23], thus allowing a more precise evaluation and diagnoses of esophageal motility abnormalities.

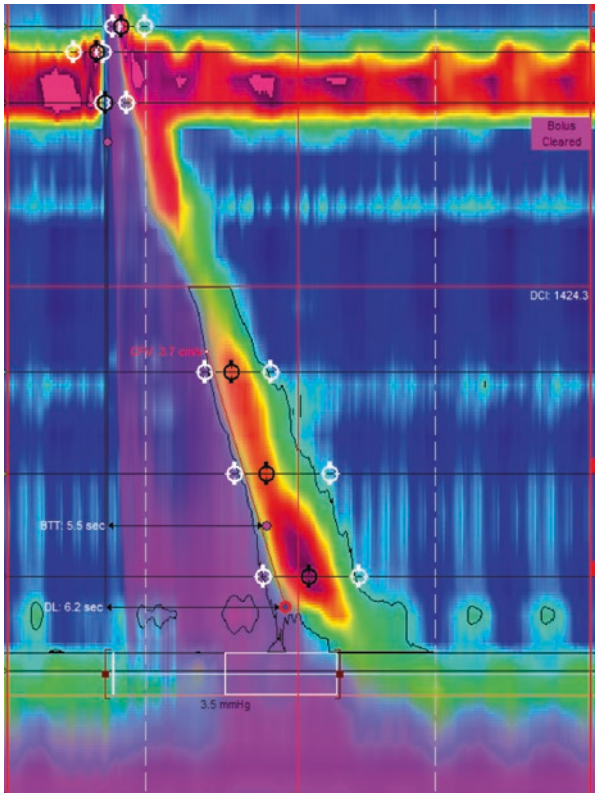

Fig. 2.2 Example of a wet swallow captured by the ManoScan™ ESO High Resolution Manometry System. The transport of the wet swallow is pictured in purple

The CC divides esophageal motility disorders based on the relaxation of the lower esophageal sphincter (LES) as characterized by the integrated relaxation pressure (IRP). Once the IRP is defined, motility disorders may be further categorized according to abnormalities of esophageal body peristalsis. In case of an elevated IRP, major disorders with an obstructed outflow are diagnosed, such as achalasia or outflow obstruction. Achalasia type I is associated with absent contractility, whereas type II involves panesophageal pressurization or type III esophageal spasm on EFT. If the IRP is above the upper level of normal and criteria of esophageal body motility exclude achalasia, an outflow obstruction is determined. In case of a normal IRP and premature contractions or a high distal contractile integral (DCI) or 100% failed peristalsis are observed, distal esophageal spasm, Jackhammer esophagus or absent contractility are diagnosed, respectively.

Minor disorders of motility that may cause dysphagia include ineffective esophageal motility (IEM), a state where the registered IRP is normal and 50% or more wet swallows are ineffective (Fig. 2.3), and fragmented peristalsis, a minor disorder that is associated with peristaltic breaks, also visible on HRM.

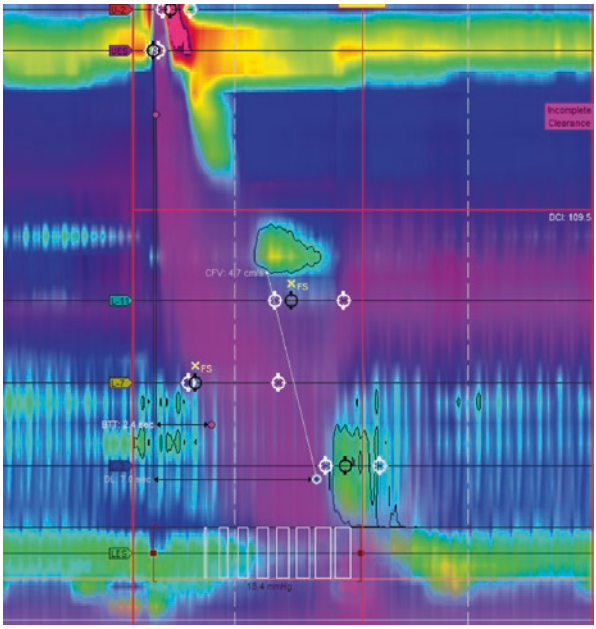

Fig. 2.3 Example of a failed swallow captured by the ManoScan™ ESO High Resolution Manometry System that is associated with an impaired bolus transport (purple)

2.4 Role of EFT Investigating Noncardiac Chest Pain

Noncardiac chest pain is described as recurrent retrosternal pain, similar to ischemic cardiac attacks, where first and foremost a cardiac cause has to be excluded [24]. Interestingly, a cohort of 212 patients experiencing chest pain revealed that after a follow-up of 1 year daily activities as well as working conditions were impaired in this group [25]. Importantly, underlying factors and disease have to be clarified. Gastrointestinal causes like GERD have to be distinguished from esophageal motor disorders, psychiatric or other causes [26]. Therefore, HRM represents a cornerstone in a complex workup process, where spastic or hypercontractile motor disorders, like distal esophageal spasm, achalasia, or Jackhammer esophagus, have to be excluded.

As far as hypercontractility is concerned, the CC offers the DCI to measure contraction vigor. Roman et al., performed HRM in 72 healthy volunteers to define a threshold for hypercontractility [27]. Given that these controls did not reach a DCI over 8000 mmHg-s-cm, this was defined to be the border of normal contractility. Swallows that exceeded this limit in manometric studies, appeared often multipeaked and were therefore nicknamed as “Jackhammer” esophagus (JE). With increasing data, single hypercontractile swallows were also observed in healthy controls. Thus, the CC v3.0 demands more than 1 hypercontractile swallow for diagnosing JE (Fig. 2.4).

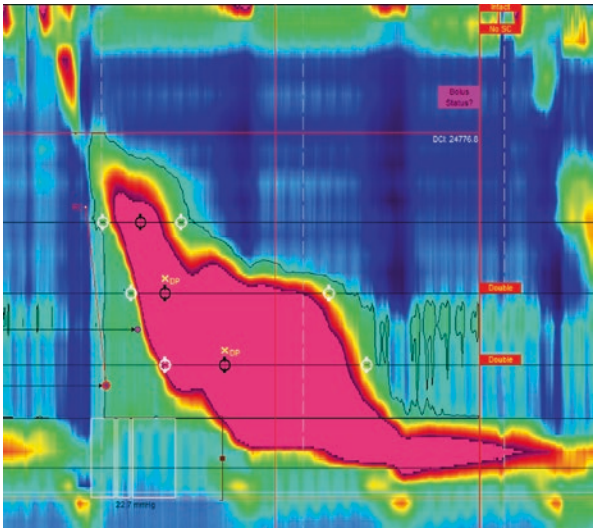

Fig. 2.4 Example of a hypercontractile swallow in a 54-year-old patient with noncardiac chest pain and dysphagia, captured by the ManoScan™ ESO High Resolution Manometry System

Kristo et al., revealed that patients with JE experienced not only noncardiac chest pain but also dysphagia, which was more frequent after a follow-up of over 2 years, indicating a progressive clinical nature of disease [28]. Interestingly, severity of dysphagia was related to the DCI in this cohort. As conditions may overlap, the same group investigated patients with typical symptoms of GERD and responsiveness to PPI therapy, which were referred with the presumed diagnosis of GERD. Interestingly, out of 2443 evaluated patients, 1.5% had JE [29]. After extensive objective testing, true GERD was observed in less than half of this selected patients. Therefore, therapeutic consequences that range from laparoscopic reflux control to peroral endoscopic myotomy have to be considered with care after HRM [30, 31].

2.5 Role of EFT for the Tailored Treatment of GERD

Although a high number of GERD patients are not satisfied with medical treatment, less then 1% of GERD patients opt for a surgical treatment. Recently, Finks et al., studied data from the Nationwide Inpatient Sample that revealed substantially decreasing numbers of anti-reflux procedures in the United States [32]. Explanatory, persisting GERD and new onset symptoms like postoperative dysphagia and gas bloating syndrome were accounted for this trend [33]. Therefore, a renaissance of anti-reflux surgery was necessary to minimize the therapeutic gap offering new procedures like magnetic sphincter augmentation, electrical sphincter stimulation, or endoscopic fundoplication [34]. As a consequence, a tailored approach was

introduced in modern surgery to select the appropriate procedure for the individual patient. Whereas various experts recommend manometry prior to surgical procedures, large surgical societies still refuse manometry as mandatory preoperative workup [12, 35].

Importantly, preoperative manometry was able to determine postoperative dysphagia and impaired quality of life after fundoplication in an analysis of 146 patients [36]. Furthermore, outcomes on wrap formation that could be tailored according to the preoperative motility status are conflicting. A large metanalysis of eight randomized controlled trials reported favorable short-term outcomes after Toupet fundoplication when compared to total fundoplication, which diminished over time [37]. Confirmatory, there were similar reflux control and adverse events, when patients were preoperatively stratified according to their motility status [38]. In contrast, Varin et al., reported that total fundoplication resulted in a significant higher incidence of reoperation and postoperative side effects when compared to partial fundoplication [39]. However, patients with motor disorders of the esophageal body are more likely to have esophageal symptoms following anti-reflux surgery [40]. Future homogeneous high-quality trials are impatiently awaited to address the issue of tailoring fundoplication according to preoperative manometric status.

As far as novel minimal invasive strategies are concerned, the status of preoperative HRM is clearer. For example, magnetic sphincter augmentation using magnetic force to reinforce the barrier against gastroesophageal reflux requires good esophageal motility noted on HRM [41, 42]. Additionally, electrical sphincter stimulation is associated with a low rate of postoperative dysphagia and is currently being tested in patients with esophageal dysmotility (NCT03476265) [43]. Therefore, limits are currently being challenged to investigate if indications of these novel procedures can be expanded, which could influence the significance of preoperative HRM [44].

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3 Endoscopy and Endoscopic Ablative Therapies in GERD and Barrett's Esophagus

Werner Dolak

3.1 Introduction

Gastroesophageal reflux disease (GERD) is a threatening condition with an increasing incidence in the Western world. Factors of Western lifestyle, such as high-caloric food intake, late meals, obesity, and smoking, are closely associated with the development of GERD, which affects approximately 20% of the general population [1]. Symptoms include heartburn or regurgitation and may also involve other organ systems, such as the larynx, the nose, or the lungs. Pathophysiologically, the disease is caused by reflux of gastric contents into the esophagus (and sometimes more proximal organs). Gastric acid, enzymes, food content, and potentially also bile are inducing an inflammatory process of the esophageal mucosa which can cause visible defects like erosions or ulcers and may lead to peptic strictures or Barrett's esophagus in the long term [2]. Barrett's esophagus is a metaplasia made up by a turnover of the esophageal squamous epithelium into a specialized intestinal epithelium containing goblet cells. It inherits a risk of malignant transformation into esophageal adenocarcinoma of approximately 0.12 to 0.4% per year, and therefore represents the most relevant precancerosis of the upper gastrointestinal tract [3, 4]. Although squamous cell cancer is still the most common histological subtype of esophageal cancer, the increasing incidence of GERD, Barrett's esophagus, and esophageal adenocarcinoma are the underlying factors by which esophageal cancer has become the most rapidly increasing cancer worldwide [5].

Endoscopy plays an essential role in both the diagnosis and treatment of GERD and associated diseases. Guidelines clearly define the role of endoscopy in the diagnostic workup of GERD [6]. Several minimally invasive endoscopic therapies for

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_3

GERD have been developed and showed very variable success rates [7]. Large population-based studies have proven the value of endoscopic surveillance for Barrett's esophagus and the effectiveness of endoscopic therapy for different grades of dysplasia arising from the Barrett's epithelium [8].

3.2 Endoscopic Assessment of GERD

According to current guidelines, endoscopy is not recommended as a first-line diagnostic approach to patients presenting with typical symptoms of GERD. A proton pump inhibitor (PPI) trial is recommended in patients without alarm symptoms such as dysphagia, weight loss, hematemesis/melena, anemia, or recurrent vomiting. Response to PPI does not necessarily prove the diagnosis of GERD, but may reduce the need for further diagnostic workup [9]. However, patients not responding to a trial of twice-daily PPI for 4 weeks or those presenting with recurrent symptoms after discontinuing drug therapy should undergo an upper gastrointestinal endoscopy to exclude mucosal defects requiring more intensive treatment. An endoscopy can also be considered in male patients over 50 years with chronic GERD and additional risk factors for esophageal carcinoma such as adipositas or smoking [6].

3.2.1 Los Angeles Classification of Esophagitis

Several classifications of GERD have been proposed. A very basic discrimination is made up by the presence or absence of erosions in the esophagus. According to the severity of mucosal lesions, erosive esophagitis can be further categorized by using a descriptive classification, such as the Los Angeles Classification supported by most gastroenterological societies (Table 3.1, Fig. 3.1) [10]. In case of nonerosive esophagitis, things become a little bit more difficult. Still, GERD can be the underlying condition responsible for the patient's symptoms. Micro-erosions might be visible on histological sections of mucosal biopsies or directly visualized in vivo by the use of confocal laser endomicroscopy [11]. However, other diagnoses, than GERD, have to be kept in mind in this situation, above all, functional heartburn, esophageal hypersensitivity, or eosinophilic esophagitis. Again, a relevant proportion of these patients will respond to PPI treatment, even a subgroup of eosinophilic

Table 3.1 Los Angeles Classification of Esophagitis [10]

Grade A	One or more mucosal breaks confined to the mucosal folds, each no longer than 5 mm
Grade B	At least one mucosal break more than 5 mm long confined to the mucosal folds but not continuous between the tops of two mucosal folds
Grade C	At least one mucosal break continuous between the tops of two or more mucosal folds but not circumferential
Grade D	Circumferential mucosal break

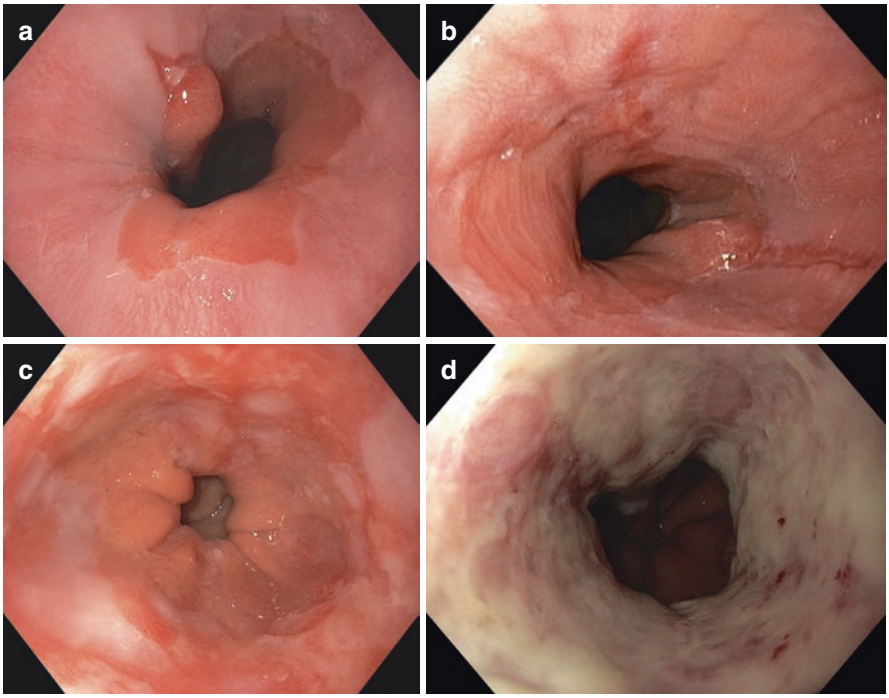

Fig. 3.1 Los Angeles classification of esophagitis. (**a**) Grade A. (**b**) Grade B. (**c**) Grade C. (**d**) Grade D

esophagitis as indicated by recent data [12]. Other diagnostic modalities such as pH-metry or impedance monitoring are helpful to further characterize difficult cases, especially in patients not or insufficiently responding to PPI treatment. Furthermore, this technique can be a valuable tool for patient selection prior to therapeutic interventions by providing reliable data on the quality and amount of gastric reflux [13].

3.2.2 Additional Endoscopic Findings in GERD

Despite the careful inspection of the esophagus for erosions associated with GERD, other macroscopic aspects can be assessed during upper gastrointestinal endoscopy: an irritation of the larynx, pharynx, and oral cavity as well as a bad dental status can be signs for a high reflux in GERD patients. Even in the absence of erosions, luminal narrowing up to stricture formation can be indicative for GERD in the esophagus. A Schatzki ring in the distal esophagus as well as a heterotopia of a gastric-type epithelium in the proximal esophagus are typical findings in patients suffering from GERD (Fig. 3.2). The latter finding can also be used as quality parameter for gastroscopy, since it should be seen in approximately 5% of all examinations [14].

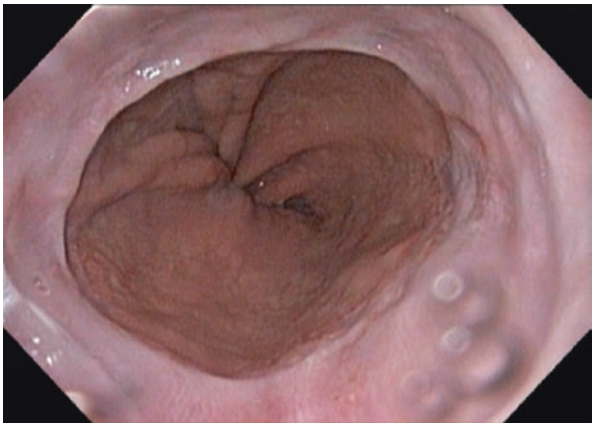

Fig. 3.2 Schatzki ring

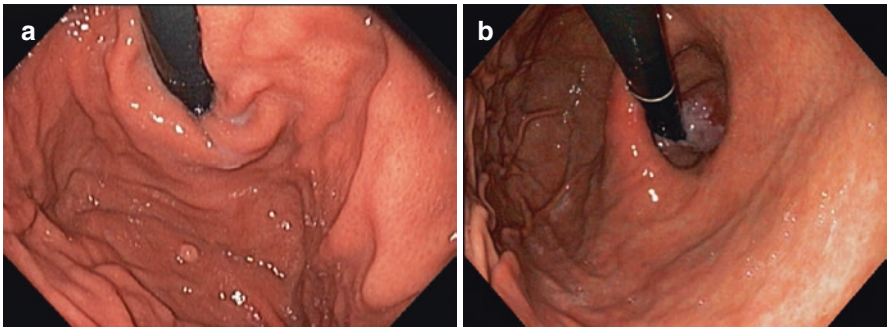

Fig. 3.3 (**a**) Hiatus without hernia Hill grade I -II. (**b**) Large hiatal hernia Hill Grade IV

Endoscopy, of course, is also a very valuable tool for the assessment of the upper gastrointestinal anatomy. Hiatal hernias as important underlying conditions of GERD can be identified, classified, and measured. Despite that, careful inspection of the esophagogastric junction including retroflex view allows to assess the angle of His and classify the anatomy according to the Hill classification (Fig. 3.3) [15]. This might be especially useful during patient selection for therapeutic interventions, since not all (minimally invasive) options are appropriate in each morphological setting. Finally, endoscopy helps to evaluate the postoperative result in patients that have undergone surgical therapy, such as fundoplication. Providing visual information on the altered anatomy, it perfectly amends other diagnostic tests in this setting, such as pH-metry, impedance monitoring, or videocinematographic studies which also evaluate dynamic aspects in this setting.

3.2.3 Biopsy Sampling in GERD

Biopsy sampling in the esophagus is generally not recommended in the diagnostic workup of GERD. Biopsies taken at the esophagogastric junction will always show some grade of inflammation at histological evaluation but the clinical value of this

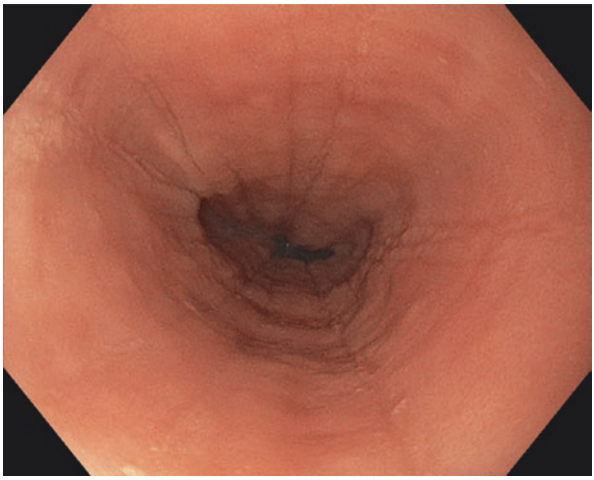

Fig. 3.4 Linear furrows, rings and withish exsudates as typical signs of eosinohilic esophagitis

finding is questionable. Some experts have proposed to take four-quadrant biopsies at three different levels of the esophagus (reflecting the reference standard for biopsy assessment in suspected eosinophilic esophagitis) in all patients with symptoms associated with GERD due to the high number of otherwise missed diagnoses of eosinophilic esophagitis (Fig. 3.4). However, this workflow is not recommended in general, especially in view of an unclear therapeutic implication [16].

3.3 Endoscopic Treatment of GERD

Over the years, various endoscopic treatments for GERD have been developed. Although hyped in the beginning, most therapies disappeared very quickly again. Only a minority of treatment options have remained on the market, some of them shared very interesting features that could also be applied to other indications. However, surgical fundoplication is still the reference standard for reconstructing an impaired esophagogastric valve as an underlying condition of GERD [17].

3.3.1 Intraluminal Fundoplication Methods

An endoscopic method that is aiming at restoring of the esophagogastric anatomy is transoral incisionless fundoplication (TIF). The EsophyX device (EndoGastric Solutions, Redmond, USA) is attached to a gastroscope and creates a gastric wrap around the lower esophagus using nonabsorbable polypropylene fasteners. It results in a 200–300° fundoplication with a valve of about 3–5 cm [18]. Concerning efficacy of the technique, a recent meta-analysis showed a pooled relative risk of response rate for TIF versus PPI/sham of 2.44 (95% CI 1.25–4.79, $p = 0.0009$) [19]. To date, no randomized controlled trials comparing the method to surgical fundoplication have been performed.

A similar concept of intraluminal fundoplication is provided by the MUSE system (Medigus Ultrasonic Surgical Endostapler, Medigus, Omer, Israel) which uses ultrasound to guide the position for intraluminal stapling in order to create an anterior fundoplication. To date, only a small number of studies have been published on MUSE. Most of them showed an improvement of GERD-related symptoms [20, 21]. However, large randomized controlled trials are lacking.

Another device is using multiple plications at the esophagogastric junction to restore the anti-reflux valve (GERDx System; G-SURG GmbH, Seeon-Seebruck, Germany). Symptom improvement and a decrease in PPI dependence could also be demonstrated for this system in initial pilot trials [22, 23]. Large trials or data on long-term efficacy are missing.

3.3.2 Endoscopic Ablative Methods

While the aforementioned techniques are aiming to create a kind of endoscopic fundoplication to strengthen the anti-reflux valve, other concepts have been developed which are not changing the anatomy of the esophagogastric junction. Among these methods, the Stretta system (Mederi Therapeutics, Norwalk, USA) has been investigated most intensively. It is a needle balloon catheter system that delivers radiofrequency ablation (RFA) energy to the muscle of the lower esophageal sphincter and the gastric cardia. Although the mechanism is not fully known to the public, the RFA energy seems to induce a hypertrophy of the muscularis propria resulting in a reduction of transient relaxations of the lower esophageal sphincter [24]. To date, several randomized controlled trials have investigated the Stretta system. While meta-analyses showed conflicting results [25, 26], a long-term follow-up study reported a 50% or greater reduction in PPI use in 64% of patients 10 years after Stretta application [27].

Another method that aims to strengthen the anti-reflux valve without changing the anatomy is based on a known side effect of endoscopic mucosal resection (EMR). The anti-reflux mucosectomy (ARMS) procedure uses wide EMR at the esophagogastric junction which results in scar formation and consequently in a reduction of reflux episodes [28]. This technique has been studied in small pilot series; large comparative trials or long-term follow-up data are missing.

In general, endoscopic anti-reflux interventions might be less invasive than conventional surgery. However, serious adverse events, such as esophageal perforation, bleeding, or pneumothorax, have been reported [29, 30]. Strict indications seem to be mandatory. Depending on the patient's anatomy and other individual factors, a tailored approach should be considered to select the appropriate treatment.

3.4 Diagnostic Approach to Barrett's Esophagus

Determining the presence of Barrett's esophagus is a setting in which biopsy sampling is generally accepted. Again, routine biopsy at the esophagogastric junction without the suspect of Barrett's esophagus on white light endoscopy is not recommended, since the histological result of intestinal metaplasia might cause

unnecessary follow-up examinations and patient's concerns. Despite histological confirmation of Barrett's esophagus, endoscopy aims to identify dysplasia within the Barrett's epithelium. Considering the fact that histological diagnosis of dysplasia is difficult in the presence of inflammation, it might be worth not to take biopsies if massive erosions or ulcers are present at initial endoscopy. Another endoscopy might then be scheduled for biopsy assessment after PPI treatment. According to recent recommendations, Barrett's esophagus should only be suspected (and verified by biopsy sampling) if the metaplastic mucosa in the distal esophagus extends at least 1 cm from the esophagogastric junction towards the oral side [31]. While this approach is for sure decreasing the number of Barrett's diagnoses and avoiding (unnecessary) surveillance, it has to be mentioned critically that dysplasia can also arise in so called ultra-short segment Barrett's esophagus (<1 cm length) [32].

3.4.1 Endoscopic Surveillance of Barrett's Esophagus

After histological confirmation of Barrett's esophagus, the first follow-up examination including careful inspection and biopsy assessment should be performed within 1 year after initial diagnosis. In this setting, endoscopy aims to detect dysplasia within the Barrett's epithelium. Targeted biopsies of irregular areas should be taken first, followed by serial biopsies according to the Seattle protocol which includes 4-quadrant biopsies in 1 or 2 cm intervals starting at the esophagogastric junction (1 cm steps in case of already detected dysplasia, 2 cm steps in non-dysplastic Barrett's) [33]. The further follow-up is based on the histological result. In non-dysplastic Barrett's, endoscopic controls are recommended every 3–5 years (depending on Barrett's length, additional risk factors). Low-grade dysplasia needs closer follow-up, in general, after 6 to 12 months, or can be considered for ablative therapy. High-grade dysplasia could be followed every 3 months, in theory. However, due to the high risk of progression most centers perform endoscopic therapy in Barrett's patients with high-grade dysplasia [34].

3.4.2 Advanced Endoscopic Imaging

To increase the diagnostic yield for dysplasia during Barrett's surveillance, a variety of strategies have been proposed: first of all, it is recommended to use the best endoscopic equipment available. Several studies clearly indicated that high-definition white light endoscopy is superior to standard definition in detecting dysplastic areas in Barrett's esophagus [35]. Chromoendoscopy can also help to detect areas of malignancy. Among topical dyes such as methylene blue or indigo carmine which are also well established in other indications, acetic acid is a cheap and effective alternative in Barrett's esophagus. By inducing a denaturation of superficial proteins, it helps to demarcate both the Barrett's epithelium and areas of dysplasia [36]. The color change over time can also be indicative for dysplasia and is a unique advantage of acetic acid in Barrett's patients [37]. Concerning optical filter mechanisms, narrow-band imaging (NBI) has clearly proven to be an effective adjuvant

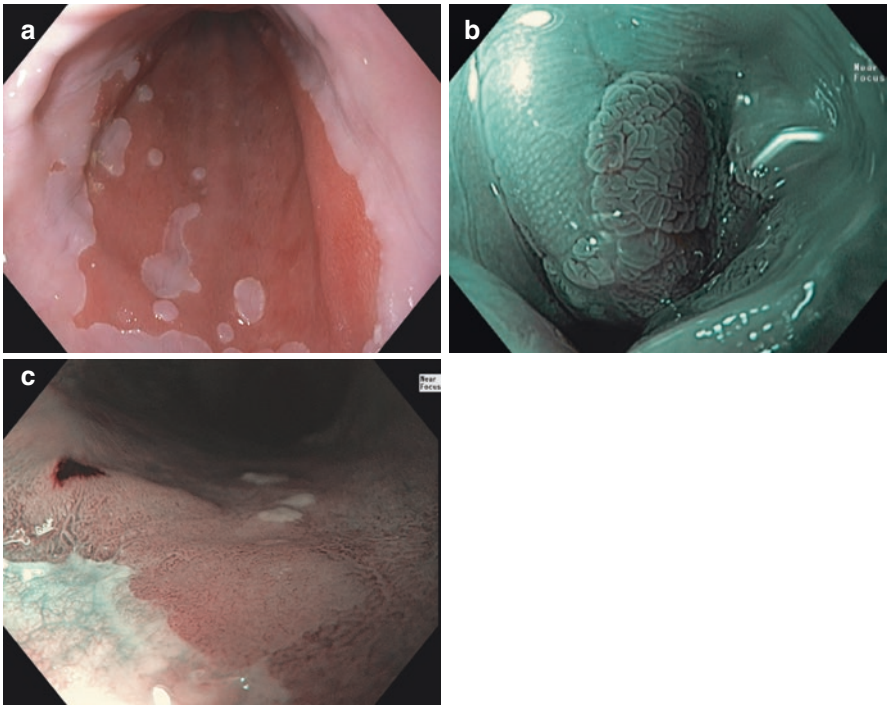

Fig. 3.5 Surveillance of Barrett's esophagus. (**a**) White light image of C0M6. (**b**) Normal surface pattern of non-dysplastic Barrett's epithelium after staining with acetic acid, NBI and near focus mode. (**c**) Irregular surface and vascular pattern of slight Barrett's cancer in NBI and near focus mode

tool for dysplasia detection. By narrowing the light spectrum to blue light at 415 nm and green light at 540 nm, NBI enables the visualization of superficial and deeper vessels, respectively (both of which are difficult to identify on normal white light imaging due to the predominance of red color in the mucosa) (Fig. 3.5) [38]. Similar results can be achieved by using virtual chromoendoscopic techniques, such as i-scan or flexible spectral imaging color enhancement (FICE). These are not based on optical filters but digital manipulation of the picture output.

More advanced endoscopic technologies such as autofluorescence imaging (AFI) [39] and confocal laser endomicroscopy (CLE) [40, 41] have shown impressive results for improving the detection or delineation of dysplasia in the setting of Barrett's surveillance. A multicenter randomized controlled trial that compared high-definition white light endoscopy plus CLE plus targeted biopsies to high-definition white light endoscopy plus random biopsies found a three-times higher diagnostic yield for the detection of neoplasia in Barrett's patient in the CLE-guided biopsy group [42]. Although such results are very promising, these technologies are still expensive and time consuming wherefore their use is mostly restricted to clinical studies or special diagnostic settings.

The following recommendations for surveillance endoscopy are rather eminence-based but still useful: the cleaning of the Barrett's epithelium before careful inspection (e.g., with addition of a mucolytic agent), the use of a distance cap (to increase visibility in very short Barrett's segments), and the topical spraying of adrenalin during biopsy sampling (to avoid visual interference by bloody oozing).

3.4.3 Discontinuing Endoscopic Surveillance

With an increasing number of (histological) diagnoses of specialized intestinal metaplasia of the esophagogastric junction, often corresponding to a hardly visible segment of Barrett's esophagus called ultra-short segment Barrett's esophagus, questions concerning the usefulness and cost-effectiveness of surveillance in this patient population have been raised. Concerning the risk of malignant progression of non-dysplastic Barrett's esophagus, the actual Barrett's length has been identified as important risk factor. Intensive efforts have been made to identify biomarkers to select those Barrett's patients that will progress to esophageal cancer. Although some recent investigations on a combination of different factors within a diagnostic marker panel have shown very promising results [43–45], the decision whether a patient should continue with endoscopic follow up for Barrett's esophagus cannot yet be based on biomarker analysis. In general, the risk of cancer decreases with every follow-up that proves a non-dysplastic status, whereas some societies proposed to apply a tailored approach to Barrett's patients and consider discontinuation of surveillance after a certain period of uneventful surveillance, absence of additional risk factors, and maybe also advanced age [31].

3.5 Endoscopic Therapy of Barrett's Esophagus Associated Neoplasia

Of note, surgery was the reference standard to treat Barrett's esophagus associated neoplasia for decades. This means that even high-grade dysplasia could have led to esophagectomy. Nowadays, endoscopy has become the first-line treatment for dysplasia and early cancer arising from Barrett's esophagus. Visible lesions within the Barrett's epithelium that are suspected of being dysplastic shall be removed by endoscopic resection. Whenever possible, en bloc resection is recommended to improve histological assessment. In case of bigger lesions, endoscopic submucosal dissection (ESD) can still provide the resection of the whole specimen in one piece. However, this technique is technically challenging, time consuming, and has a higher risk of complications. In the setting of Barrett's associated neoplasia, endoscopic mucosal resection (EMR) is therefore recommended as method of choice by the European Society of Gastrointestinal Endoscopy (ESGE) [31]. Whereas this recommendation is supported sufficiently by present data [46], ESD might be still a valuable alternative in experienced hands [47].

In case of dysplasia detection on random biopsy that cannot be associated to a visible lesion, endoscopic ablative treatment is recommended. After endoscopic resection of visible dysplastic lesions, it is also recommended to remove the remaining Barrett's epithelium by an ablative method in order to minimize the risk for metachronic dysplasia [31]. Although endoscopic resection of the entire Barrett's epithelium could be performed alternatively, ablative therapy is superior in terms of late adverse events such as stricture formation. The most commonly used endoscopic ablative therapy in Barrett's esophagus is now radiofrequency ablation (RFA). Argon Plasma Coagulation (APC) is a safe and effective alternative that has been investigated in one of the largest series of endoscopically treated Barrett's neoplasia [46]. However, in case of long segment Barrett, the technique is somehow cumbersome. In this setting, it has been proposed to be used in combination with submucosal injection termed as hybrid APC [48]. Photodynamic therapy has been used in former times but has become outdated meanwhile due to high rates of post-treatment strictures [49]. Cryo-ablative therapy is another promising technique that is currently under investigation in several studies [50].

3.5.1 Endoscopic Mucosal Resection

EMR is a kind of polypectomy. In opposite to pedunculated or sessile lesions, most dysplastic areas in Barrett's esophagus are flat. Such lesions, mostly corresponding to the 0-II category of the Paris classification (0-IIa flat elevated, 0-IIb flat within the surface level, 0-IIc flat depressed) [51], cannot be resected by simple snaring but require more advanced tools. The goal of resection is to lift these lesions from the other layers in order to avoid injury to deeper tissue. In EMR, lifting is achieved by submucosal injection with, e.g., saline solution to create a submucosal cushion. The (artificial) polyp can then be snared "en bloc" (within one piece) or in "piece-meal technique" (several pieces). The most important risks of EMR are bleeding and perforation. If the lesion does not lift adequately, this might be diagnostic for deeper invasion, also known as the "non-lifting sign" [52].

Depending on the location and size of the lesion, a piece-meal approach might be easier and safer by means of a lower risk of perforation. However, as orientation of pieces is difficult, definite statements on the completeness of resection by histological evaluation are not possible. Histological staging is further limited by lack of information about the area close to the cutting edges of the specimens (which could have shown vascular invasion, for example). Finally, due to the risk of remaining tissue bridges on the resection ground, recurrence rates after piece-meal resection are generally higher than after en bloc resection [53].

Within the past decades, several distinct EMR kits have been developed to improve performance of resection and simplify the resection technique, especially in the upper GI tract. Cap-assisted EMR is now widely used for resections in the esophagus, including treatment of Barrett's esophagus. A cap attached to the distal tip of the endoscope is used to target the lesion, then suction is applied (with or without previous submucosal injection) to lift the mucosa into the cap where it is

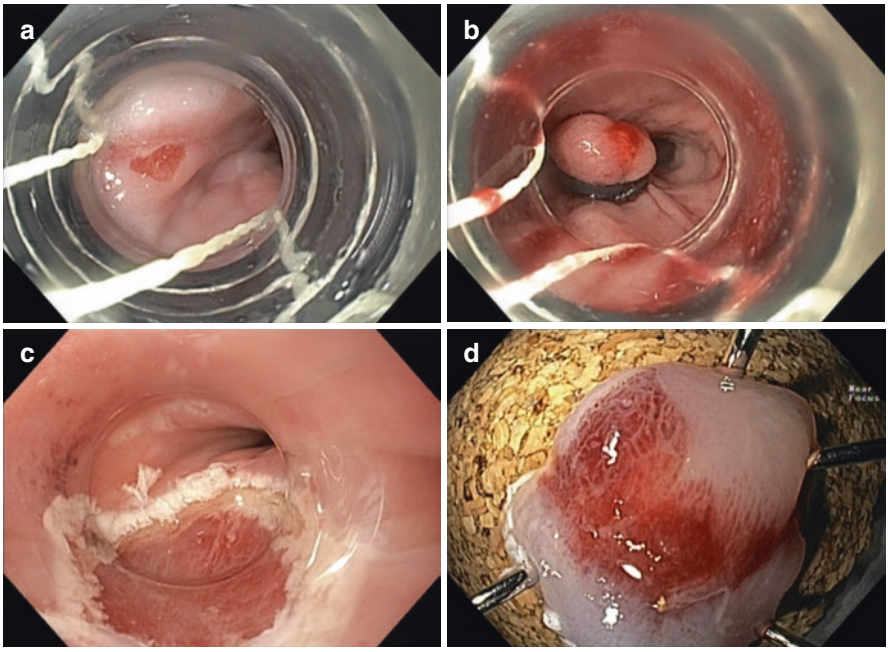

Fig. 3.6 Band ligation EMR of small Barret's cancer. (**a**) Targeting the lesion for rubber band placement. (**b**) Rubber band placed below the lesion. (**c**) Wound after snaring the lesion below the rubber band. (**d**) Resected specimen

caught by a previously expanded snare. After stopping suction, the specimen can be clearly seen again to assure appropriate snare placement. Finally, current applied to the snare will lead to cutting of the lesion. Like conventional EMR, the cap-assisted technique can be performed either for en bloc or for piece-meal resections (Fig. 3.6) [54].

An even easier applicable EMR kit provides rubber bands mounted on the distal cap that can be released via a wire comparable to band ligation for esophageal varices. After suction of the lesion, one of the bands is released to capture it. The snare is then placed below the band to cut the specimen [55]. In theory, band-ligation–assisted EMR is safer than direct snaring since the band is not tight enough to capture deeper layers, such as the muscularis propria (which would result in perforation). In practice, however, this shortcoming of direct snaring can be overcome by a simple trick: prior to cutting, the snare can be reopened just a little bit after capturing the specimen to guarantee that any muscular fibers are released [56].

3.5.2 Endoscopic Submucosal Dissection

Since EMR has a technical limit for en bloc resection (made up by the size of the cap, for example, or by the dimension of the snare that can be used with an

acceptable risk of complications), another endoscopic resection technique has been developed in Japan at the beginning of the new millennium. This method is called "endoscopic submucosal dissection" (ESD) [57]. By providing en bloc resection of greater depth and unlimited lateral size (in theory), it can achieve curative R0-resections of larger malignancies. However, to achieve oncological clearance, many additional factors have to be considered despite technical success of complete resection. As the risk of metastasis increases with depth of invasion, (lympho-)vascular involvement and undifferentiated tumor grade, a so-called "salvage" surgery can still be beneficial despite complete endoscopic resection of the primary tumor to assess the surrounding lymph nodes [58]. Nevertheless, even in borderline lesions that are suspected to show one of the mentioned features of advanced malignancy, ESD is (in theory) superior to EMR by means of diagnostic information provided, as the pathologist will still get a more complete specimen for detailed evaluation. By means of therapy, ESD led to the extension of the morphological criteria of certain malignancies that can still be treated endoscopically (Fig. 3.7) [59].

ESD is technically more challenging than EMR, which makes it also difficult for beginners. As for EMR, the lesion has to be lifted from deeper wall layers by submucosal injection of, e.g., saline solution. However, the resection itself is different, since there is no "blind" snaring but an active dissection below the lesion performed step-by-step within the submucosal space under direct visualization. A transparent hood attached to the distal tip of the endoscope helps to keep clear vision of the resection plane. The dissection itself is performed with a special ESD knife. There are several devices on the market that have been optimized for different locations and also for special procedures that have been developed on the basic principle of ESD. Hybrid instruments are equipped with a water-jet function that allows injection of fluid into the submucosal space without exchanging the instrument. As for EMR, bleeding and perforation are the main treatment emergent adverse events. Both can occur during the procedure or late term. Intra-procedural complications are often the result of less experience—submucosal vessels could be predicted and coagulated prior to unintended dissection, perforation is often caused by cutting at the wrong tissue plane—however, if identified correctly, these complications can be managed easily with adequate skills. Late-term adverse events, on the other hand, are highly dependent on the size of the resection and the respective location. Coagulation of visible vessels in the remaining submucosa can reduce the risk of bleeding after ESD, and prophylactic clipping can be considered to avoid perforation secondary to, e.g., toxic injury of the wound by bile or pancreatic juice in the duodenum [60].

In opposite to EMR, ESD has not yet become a standard technique of endoscopic resection in the Western world. Although there are many courses to learn the technique, ESD is still limited to very specialized endoscopic centers here. This has several reasons. On the one hand, ESD requires a long learning curve, resulting in severe adverse events like bleedings or perforations at the beginning [61]. But lesions that would be ideal for training are very rare outside of Asia due to the lack of gastric cancer screening programs, for example. On the other hand, even after sufficient training, lesions that would justify an ESD are rather limited in the Western world. Early gastric cancer, as the leading indication for ESD in Asia, is

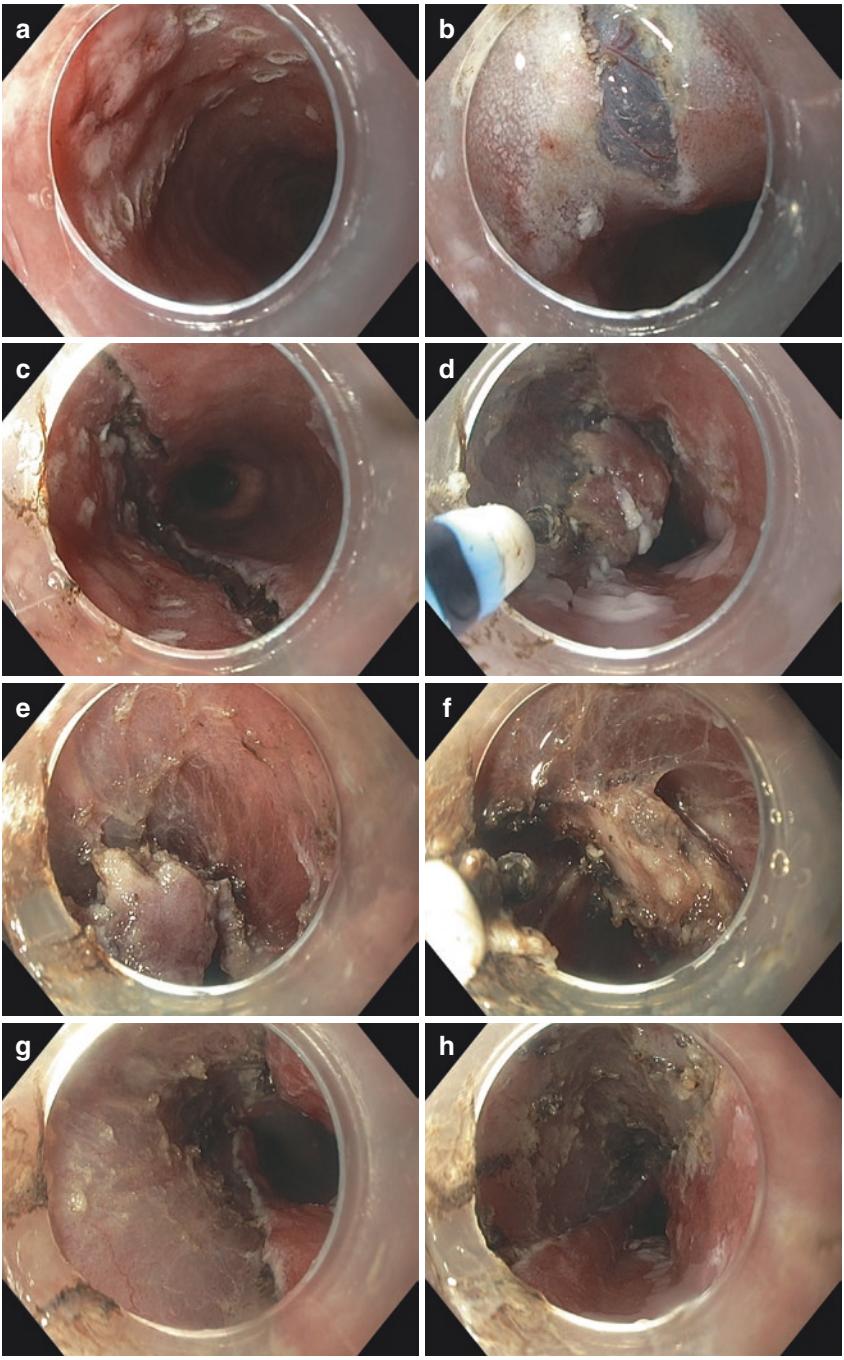

Fig. 3.7 ESD of Barrett's cancer. (**a**) Marking around the lesion. (b) Starting circular mucosal incision. (**c**) Completing circular mucosal incision. (**d**) Starting submucosal dissection. (**e**) Ongoing submucosal dissection. (**f**) Finishing submucosal dissection. (**g**) Wound after completed submucosal dissection showing vessels. (**h**) Wound after coagulation of remaining vessels. (**i**) Resected specimen

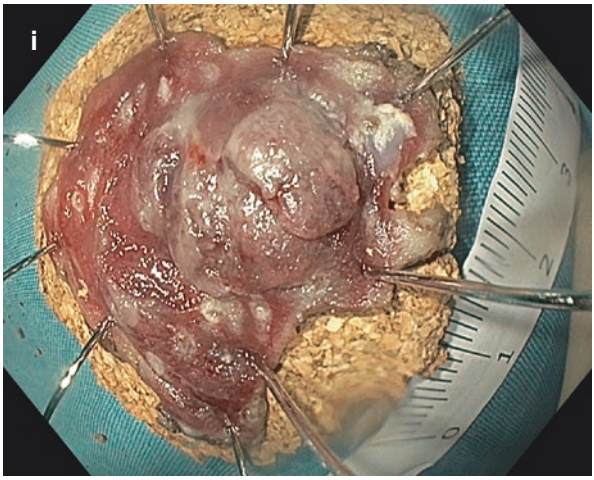

Fig. 3.7 (continued)

hardly detected in the west, not only due to the much lower incidence but also due to the lack of awareness and knowledge in the absence of comparable screening programs. Similar shortcomings can be mentioned for squamous cell cancer. In opposite to that, Barrett's esophagus–associated neoplasia becomes more frequently detected during Western surveillance programs. However, for this malignancy, big series have shown that treatment also with EMR can achieve good long-term results [46]. Finally, there are lots of colonic lesions found in the Western patient population. However, given the even higher risk of ESD at that site (except for the lower rectum), it is also difficult to establish the technique there and so, and those lesions that cannot be treated curatively by EMR (e.g., laterally spreading tumors of non-granular type) might still end up with surgery in most Western hospitals [62].

3.5.3 Radiofrequency Ablation

Radiofrequency ablation uses high-frequency current that is applied to different ablation catheters to achieve thermal destruction of the Barrett's epithelium. A 360° balloon catheter can be used for circumferential treatment, 90° catheters of different length can be applied to treat single tongues of Barrett's epithelium, and a through-the-scope catheter can be used for areas that are difficult to target by other devices, e.g., in the presence of esophageal stricture (Fig. 3.8). RFA has shown excellent results by means of eradication of dysplasia and sustained eradication of Barrett's metaplasia [63, 64]. Recent studies also suggested to use RFA to treat low-grade dysplasia that has been confirmed by a reference pathologist due to the high risk of malignant transformation [65]. In comparison to wide endoscopic resection, RFA has a low risk of stricture formation of about 5% and a good safety profile [66]. Post-EMR strictures, persistent reflux esophagitis, or narrow esophageal lumen have been identified as predictors of moderate treatment response to RFA [67].

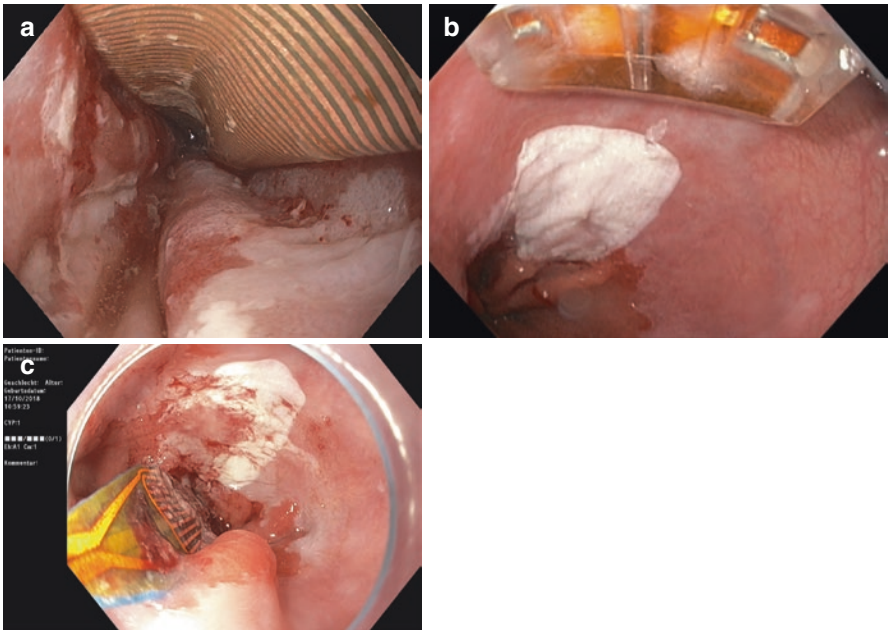

Fig. 3.8 Radiofrequency ablation. (**a**) Barrx 360 express RFA balloon catheter (deflated) for treating long segment Barrett's esophagus. (**b**) Barrx 90 RFA focal catheter for treating single mucsoal tongues of Barrett's esophagus. (**c**) Barrx channel RFA catheter for narrow lumen treatment

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GERD and Barrett's Esophagus: Ablative and Non-Ablative Therapies

4

George Triadafilopoulos

4.1 Introduction

Over the past decade, the development, availability, and expanding application of many novel endoscopic treatment modalities have led to a dramatic modernization of the management of patients with gastroesophageal reflux disease (GERD) and Barrett's Esophagus (BE). It is well established that GERD may progress to BE with or without low- or high-grade dysplasia and, subsequently, esophageal adenocarcinoma (EAC); the prevalence of EAC is increasing more rapidly than any other malignancy. In contrast, GERD is not a risk factor for esophageal squamous cell dysplasia and carcinoma (ESCC), which are more prevalent worldwide but less prevalent in the Western world than Barrett's dysplasia and EAC [1]. Regardless, the global burden of these diseases is increasing, impacting on morbidity, quality of life, mortality, and health care costs.

Over the past two decades, the use of radiofrequency (RF) for the treatment of GERD-related esophageal diseases has rapidly expanded and validated. RF ablation of BE dysplasia (*Barrx, Medtronic, Sunnyvale, CA, USA*) aims at complete eradication of dysplasia and surrounding metaplasia, while the Stretta procedure (*Mederi Therapeutics, Inc., Greenwich, CT, USA*) treats the muscle of the gastroesophageal junction (GEJ), aiming at reducing the magnitude of acid reflux without an effect on the mucosa [2, 3]. (Fig. 4.1). The former is a cancer risk reduction strategy without any impact on GERD symptoms, while the latter is mostly addressing symptomatic relief and carries no known impact on EAC prevention. If there is no significant sliding hiatal hernia, the two RF procedures may be combined in any given patient.

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_4

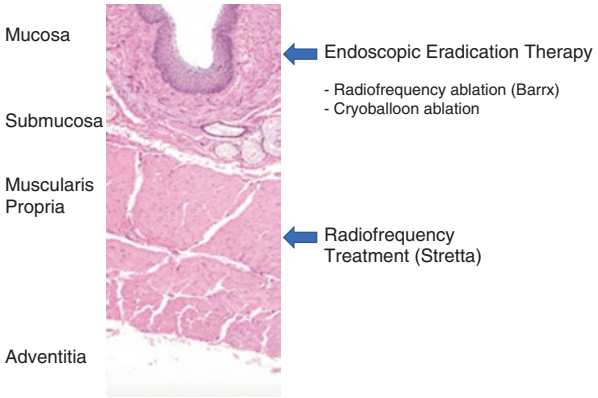

Fig. 4.1 Diagrammatic depiction of the targets of endoscopic eradication therapy (EET) and radiofrequency (Stretta). The former, utilizing either radiofrequency energy (Barrx) or cryoballoon ablates the precancerous mucosa without affecting the submucosa or muscularis propria, and it is a cancer prevention strategy. In contrast, the latter applies RF energy to the muscularis propria with minimal, if any, effect on the mucosa, aiming to altering the gastroesophageal junction compliance thereby minimizing esophageal acid exposure and reducing or eliminating GERD symptoms

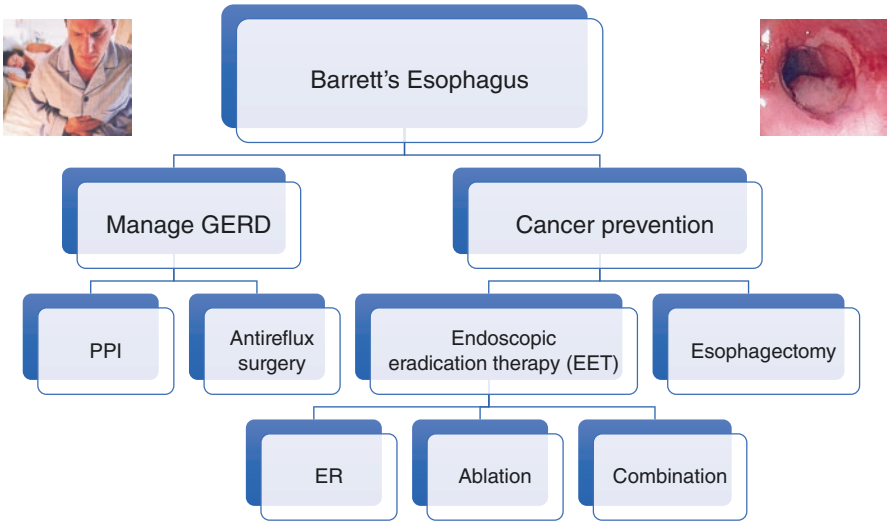

Fig. 4.2 Outline of the management of Barrett's esophagus that highlights control of GERD as an important background element and cancer prevention as the key objective for cancer prevention. Pharmacologic, endoscopic, and surgical approaches are used as needed based on individual clinical phenotypes

However, proton pump inhibitors (PPI) are used as an adjunct measure in Barrx ablation because they control GERD symptoms, prevent BE recurrences, and possibly have a chemoprevention role against EAC. Anti-reflux surgery may also be used as adjunctive therapy to ablation because it repairs the hiatus and prevents acid reflux (Fig. 4.2). More recently, with its low cost and better tolerability profile,

cryoballoon ablation (*C2 Therapeutics, Redwood City, CA, USA*) has been introduced, aiming at complete eradication of dysplastic BE. This cancer management approach is also combined with PPI or anti-reflux surgery for GERD.

4.2 Endoscopic Eradication Therapy

In general, endoscopic eradication therapy (EET) for dysplasia, be it with Barrx or cryoballoon, is used as an alternative to esophagectomy, a procedure associated with significant morbidity and mortality and a negative impact on quality of life, which is nowadays reserved for patients with submucosal invasion and high risk for lymphatic involvement (Fig. 4.2). Endoscopic eradication therapy (EET) for dysplastic Barrett's esophagus (BE) comprises resection and mucosal ablation techniques, either alone or in combination. Over the years, these techniques have been tried with success, not only for dysplastic Barrett's epithelium but also for non-dysplastic Barrett's epithelium and early adenocarcinoma. Endoscopic resection is usually carried out for visible lesions, either as endoscopic mucosal resection (ER), which is practiced widely in Western countries, or as endoscopic submucosal dissection (ESD), which is more popular in Japan and throughout Asia. Therefore, the management of BE is driven by (1) the presence or not of submucosal disease that renders EET an inappropriate option for cancer management and by (2) the endoscopic recognition of dysplasia, which, if present, defines with need for endoscopic resection. Only after the BE surface has been rendered flat, the mucosal ablation strategies (Barrx or cryoballoon, or both in tandem) come into play (Fig. 4.3).

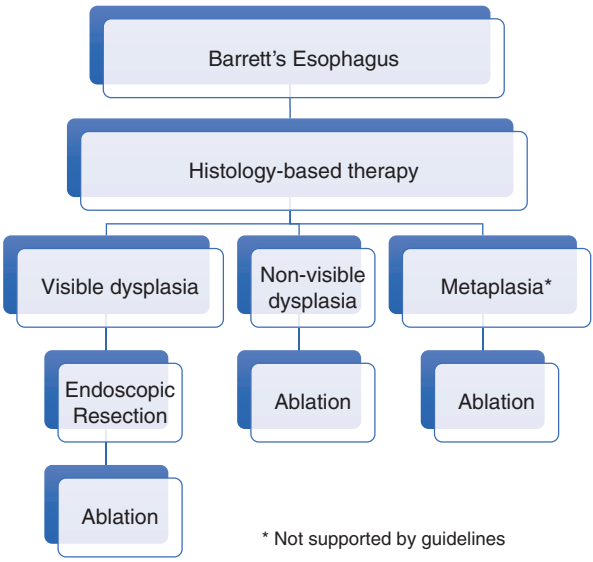

Fig. 4.3 Endoscopy- and histology-based outline of management of Barrett's esophagus aimed at dysplasia reversal and elimination of cancer development

4.3 Radiofrequency Ablation for Barrett's Dysplasia

The Barrx ablation system includes an energy generator and several ablation catheters that precisely control the depth and extent of RF ablation. The catheters include the self-adjusting 360 Express balloon/catheter for circumferential (360°) treatments of 3 cm length segment, the channel (TTS) catheter, that delivers RFA through the working channel of an endoscope, and the 60, 90, and ultra-long focal ablation catheters that are mounted on the tip of the endoscope to deliver focal energy to variable mucosal lengths.

In a pivotal multicenter RCT, 127 patients with BE-related neoplasia (63 patients with HGD and 64 patients with LGD) were either treated with RFA or underwent a sham procedure [4]. Patients were treated every 2 months, with end points assessed at 12 months. In the intention-to-treat analysis, 90.5% of those with LGD had neoplasia eradication, compared to 22.7% in the sham group. Similarly, 81% of patients with HGD had complete eradication of dysplasia, compared to 19% in the sham controls; 77.4% of patients had complete reversal of intestinal metaplasia (CR-IM), compared to 2.3% in the sham group. The progression rate of HGD to cancer was significantly lower in those treated with RFA, compared to the sham group (2 and 19%, respectively). In another retrospective study of 244 patients with BE-related neoplasia treated with RFA, CR-IM was achieved in 80% and CR-D was achieved in 87% of patients. Cancer developed in only four cases [5]. In a large European series, 132 patients underwent EMR with pathology showing invasive cancer ($n = 78$), HGD ($n = 31$), LGD ($n = 7$), no dysplasia ($n = 3$), and no EMR ($n = 13$). After a median of three treatments with RFA, intention-to-treat analysis CR-D was achieved in 91% and CR-IM in 88% of patients. Of the five patients not reaching CR-D, one was referred for surgery for T1sm1, G2 cancer and four patients continued with endoscopic therapy [6]. A UK RFA registry evaluated 335 patients with BE-related neoplasia (72% with HGD, 24% with intramucosal cancer, 4% with low-grade dysplasia). Visible lesions were removed by ER, followed by RFA every 3 months. The authors found CR-HGD in 86% of patients, CR-D in 81%, and CR-IM in 62% of patients at 12 months. Invasive cancer developed in 10 patients (3%), and disease progression was seen in 5.1%. Symptomatic strictures developed in 9% of patients and they were treated with endoscopic balloon dilation [7]. A meta-analysis of recent studies of patients treated with RFA identified 18 studies with 3802 patients reporting efficacy and 6 studies of 540 patients with long-term durability. CR-IM was achieved in 78% of patients while CR-D was achieved in 91% [8].

A multicenter RCT with 136 patients with low-grade dysplasia equally randomized treatment with RFA or endoscopic surveillance. Those treated with RFA had a 25% reduction in the risk of progression to high-grade dysplasia (1.5% for RFA vs. 26.5% surveillance) and cancer progression by 7.4% (1.5% RFA vs. 8.8% surveillance). In the treatment cohort, neoplasia eradication was 92.6% and IM reversal was 88.2%, compared with 27.9% for dysplasia and 0.0% for IM among those in surveillance [9]. A summary of these studies' data is shown in Fig. 4.4.

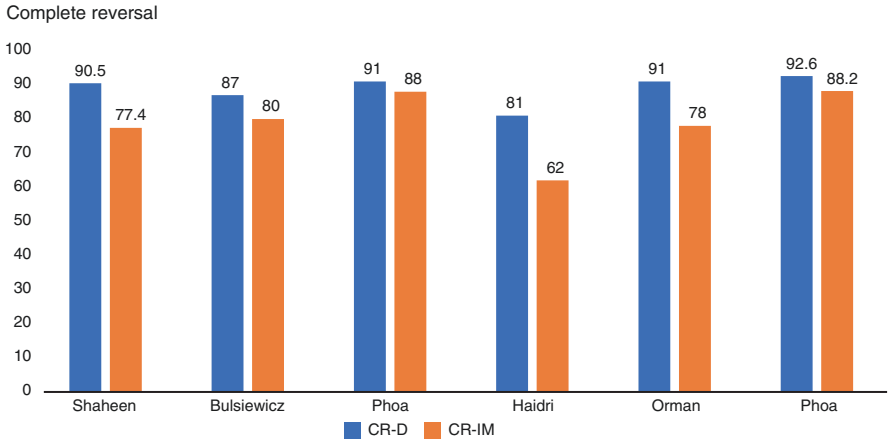

Fig. 4.4 Summary of the efficacy data of six leading studies (of variable design) using radiofrequency ablation to completely reverse dysplasia and metaplasia in patients with dysplastic Barrett's esophagus

4.4 Cryoballoon Ablation for Barrett's Dysplasia

Cryotherapy is designed to deliver a high rate of thermal energy transfer by using nitrous oxide effectively snap-freezing the tissue and resulting in immediate cell death. The focal cryoballoon ablation (FCBA) system comprises a through-the-scope (TTS) catheter with a conformable balloon that obviates the need for sizing, a handle and a small disposable cryogen cartridge. The balloon is simultaneously inflated and cooled with nitrous oxide from the cartridge, resulting in focal ablations of approximately 2 cm^2. FCBA is easy to use and requires no capital equipment. FCBA of BE islands is also quite effective. In a recent study with 30 patients, complete eradication of intestinal metaplasia and dysplasia was observed in 100% of the completely ablated areas without stricture formation [10].

In a single center, prospective, single-arm trial, 40 BE patients with confirmed low-, high-grade dysplasia, and early neoplasia (LGD, HGD, T1aECA) without prior therapy ("treatment naïve"), or persistent/recurrent disease despite prior therapies ("previously ablated"), were treated with FCBA at a dose of 10 s of ice per site. EMR was performed prior to cryoablation. Treatments were repeated every 10–12 weeks until eradication of intestinal metaplasia (IM). After 1 year, complete response rates were 92% for dysplasia and 84% for IM. No perforations occurred. One patient was hospitalized for bleeding. Post-ablation pain requiring narcotics was reported in 23%, none lasting >24 h. Four patients developed inflammatory stenosis (2 requiring interval dilation and 1 in preexisting stricture), yielding stricture incidence of 5%. The authors concluded that FCBA is a promising, safe, and potentially effective primary or rescue endoscopic treatment for BE-associated neoplasia [11]. Larger, multicenter trials are underway.

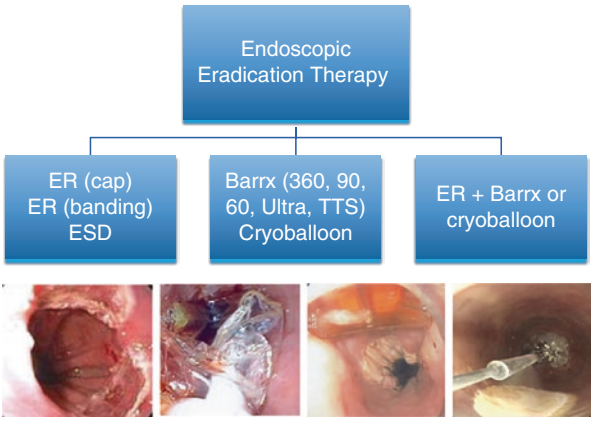

Fig. 4.5 Outline of the options available for endoscopic eradication therapy. The bottom photographs (left to right) depict endoscopic resection, 360° radiofrequency balloon ablation, focal radiofrequency ablation, and cryoballoon ablation

A well-accepted and widely used model of EET is shown in Fig. 4.5. First step is to ascertain that any nodularity is resected for diagnostic (staging ER) and therapeutic purposes, using the cap method of ER or the suck and cut (banding) for lesions less than 2 cm diameter, or ESD for larger surface resections. If resection is inadequate in addressing the entire BE segment surrounding dysplasia, then Barrx (focally or circumferentially) or cryoballoon focal ablation are used to complete reversal of metaplasia and dysplasia. In cases of flat dysplasia, the entire BE surface is treated by ablation, again aiming at complete reversal.

4.5 Radiofrequency Treatment for GERD (Stretta)

The Stretta procedure, an RF application to the lower esophageal sphincter (LES), is an endoscopic alternative to chronic medical therapy or surgery for GERD [12]. Since its introduction, more than 15 years ago, many improvements have facilitated its use and safe and effective application in patients with GERD who do not have a significant (>2 cm) sliding hiatal hernia. Stretta does not ablate the epithelium of the esophagus, but instead treats the esophageal muscle layer straddling the GEJ, resulting in thickening of the LES, decreased frequency of transient LES relaxations, and thereby reducing pathologic esophageal acid exposure (Fig. 4.1). Stretta is performed on an outpatient basis, under conscious sedation, using standard endoscopy to assess the GEJ and a proprietary catheter that is connected to a radiofrequency delivery module based on predetermined algorithm that minimizes mucosal damage while it maximizes proper energy delivery to the muscle, based on temperature and impedance (Fig. 4.6). Earlier concerns about adverse events, such as esophageal stricture formation or neurolysis, have been refuted over time.

Two recent meta-analyses examined the impact of Stretta on objective and subjective end points yielding conflicting results. Perry et al., performed a meta-analysis of randomized controlled trials (RCTs) and cohort studies that included a total of 1441 patients from 18 studies [13]. They demonstrated that Stretta significantly

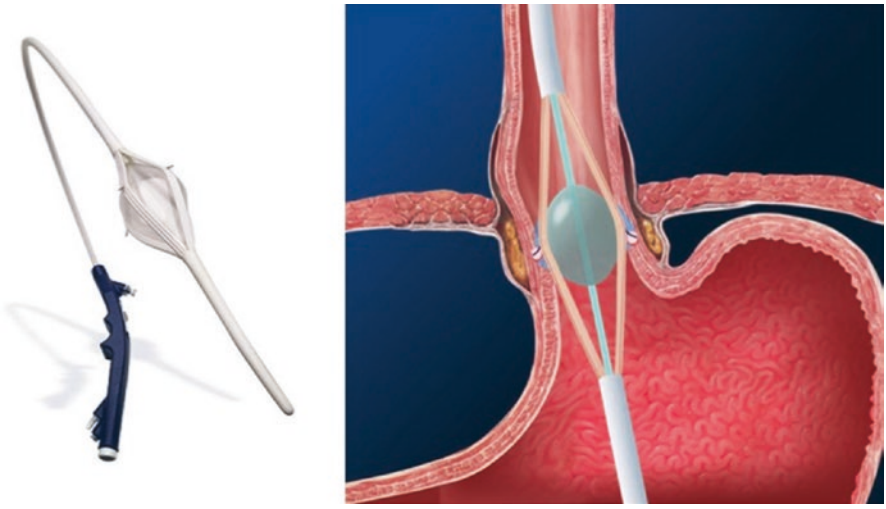

Fig. 4.6 (Left), The Stretta balloon/catheter that is used to deliver RF energy to the muscle of the GEJ. (Right), Diagram of the treatment effect; when the balloon is inflated and the four needles deployed the energy in delivered selectively to the muscle and not the mucos

improved heartburn, health-related quality of life (HRQL) scores, and esophageal acid exposure. Lipka et al., in another meta-analysis, only included 165 patients from four trials [three Stretta vs. sham and one Stretta vs. proton pump inhibitor (PPI) treatment]. While cautioning about the poor quality of the available evidence, the authors showed no differences in clinical outcomes of Stretta versus sham or PPI treatment. There was no significant improvement in % time pH <4, LES basal pressure, ability to stop PPI or HRQL RCTs [14]. The authors concluded that Stretta does not result in significant clinical or physiological changes, as compared with sham therapy.

Another systematic review and meta-analysis of both randomized controlled trials (RCTs) and cohort studies assessed the use of Stretta in GERD, using calculations by both fixed and random effects modeling and generalized inverse weighting for all outcomes and concluded that Stretta is efficacious in improving both objective and subjective clinical endpoints [15] (Fig. 4.7). Twenty-eight studies (4 RCTs, 23 cohort studies, and 1 registry) representing 2468 unique Stretta patients were included. The mean follow-up time was 25.4 months. Their pooled results showed that Stretta improved HRQL by −14.6 and heartburn scores by −1.53. After Stretta, only 49% of the patients using proton pump inhibitors (PPIs) at baseline required PPIs at follow-up. Further, Stretta reduced the incidence of erosive esophagitis by 24% and esophageal pathologic acid exposure by a mean of −3.01. LES basal pressures were increased by a mean of 1.73 (Fig. 4.7) Stretta may also result in significant cost savings, ranging from 7.3 to 50.5% in the post-procedure 12-months, supporting the utilization of Stretta in clinical practice as an alternative therapy for GERD patients without hiatal hernia who are seeking non-surgical options [16].

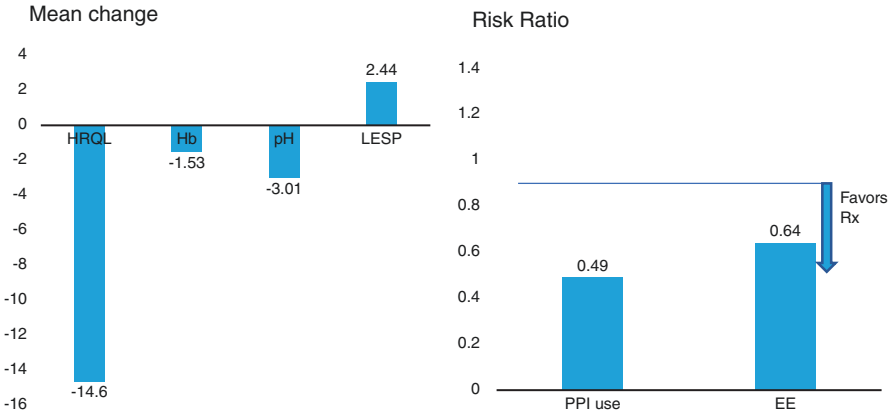

Fig. 4.7 Summary of the Stretta effects as published in a recent meta-analysis [15]. (Left), Mean change of Stretta effects on HRQL, heartburn scores, acid exposure, and LES pressure, all revealing favorable effects. (Right), Mean risk ratios after Stretta, demonstrating favorable effects of therapy on PPI use and prevalence of erosive esophagitis post-procedure

4.6 Conclusions

The efficacy and safety of ablation in combination with endoscopic resection in the treatment of patients with dysplastic and early neoplastic BE have replaced the previous models of esophagectomy or intensive surveillance. Such therapeutic options, matched with enhanced optical and digital tools that facilitate the diagnosis, have revolutionized the field which increasingly interfaces clinicians, endoscopists, surgeons, and pathologists towards a common goal, that of cancer prevention. At the same time, the treatment of the GEJ by radiofrequency may control GERD for many who are refractory to PPI therapy and are unwilling to undergo anti-reflux surgery and for those who are concerned about long-term, PPI-related, adverse events.

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Radiology of Benign Gastroesophageal Reflux Disease (GERD)

5

Marcel O. Philipp

5.1 Introduction

The following is not intended as radiologic textbook of how to perform examinations of the upper gastrointestinal tract, or how to interpret the images obtained with those examinations, which can be found elsewhere in excellent quality [1–3], but as more general considerations on what can and should be seen with regard to possible sources of error and which questions should finally be answered. From the radiologist's point of view, the imaging of the esophagus is a beacon of the decline of barium studies, which may be at least partially the radiologists own fault in turning their attention disproportionally to cross-sectional imaging and neglecting refinement of barium studies and training of radiologists to perform and interpret those studies despite the knowledge that they are highly operator dependent [4]. Nevertheless, fluoroscopy with magnetic resonance imaging (MRI) is a promising tool in the evaluation of swallowing disorders, dysphagia, esophageal motility, morphology and function of the gastroesophageal junction (GEJ), and gastroesophageal reflux disease (GERD), lacking the use of radiation but with substantial higher costs and limited availability [5–10].

Radiologic imaging should always be performed to answer clinical questions and to establish a diagnosis, thus using the appropriate modality in a highly sophisticated way, which means understanding of the imaging methods strengths and limitations. Therefore, profound knowledge of technique and disease, including pathogenesis and therapy, and collaboration and communication between clinician and radiologist are essential. From this perspective imaging must not be an end in itself but has to perform its role given by standard operating procedures and guidelines. Following international guidelines [11, 12], radiologic imaging methods do not play a role anymore in the establishing of the diagnosis of GERD in adults when

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presenting with typical symptoms such as heartburn, regurgitation, and chest pain. Although barium esophagram is a well-established and useful tool in imaging of diseases of the esophagus [1], despite the use of ionizing radiation, it is outrun as for sensitivity and specificity by endoscopy, esophageal manometry, and pH monitoring [13]. This is even true when using special techniques as, for example, the water syphon test [14] or the Valsalva maneuver. But barium esophagram certainly plays a role when additional symptoms, mostly dysphagia [15], are present, and surgery is planned in order to establish a functional and anatomical nadir [16, 17]. It is the first-line imaging tool for postoperative control and visualization of short- and long-term complications after surgery [18]. Following the American College of Gastroenterology's definition of gastroesophageal reflux disease [11] as "… symptoms or complications from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung," radiologic imaging is also useful for the visualization of disease-related complications prior to surgery such as aspiration.

So imaging of the upper gastrointestinal tract may not be necessary to establish the diagnosis of GERD, but is an important fast, noninvasive, and readily available tool to depict and diagnose complications and additional pathologies ahead of surgery, such as swallowing disorders, shortened esophagus, esophageal dysmotility, eosinophilic esophagitis, hiatal hernias, and achalasia [19–24]. In addition, it is an important postoperative diagnostic tool, especially in symptomatic patients.

5.2 Imaging Before Anti-Reflux Surgery

Double-contrast esophagography and dynamic swallowing studies [1, 3], videofluoroscopy, using barium and ionizing radiation, are still the most requested imaging modalities in patients with dysphagia, but MRI also shows promising results [25]. Dysphagia [26, 27] is a common problem especially in the elderly and known to be more common in patients with GERD. Other reasons mostly include neurologic disorders such as stroke or Parkinson disease. Oropharyngeal dysphagia is more common in the latter patients, however substernal dysphagia is more often seen in patients with diseases of the esophagus and the proximal stomach. The advantage of imaging studies in those cases is the simultaneous depiction of functional and structural disorders and therefore providing the surgeon with a clear image of what to expect during surgery. GERD, in patients with or without dysphagia, frequently causes typical changes to the esophageal mucosa. Inflammatory changes with reflux esophagitis are seen as granular radiolucencies with indistinct borders, which extend from the gastroesophageal junction (GEJ) upward. With prolonged exposition of the esophageal mucosa to gastric acid localized ulcerations can be seen as linear or stellate opacities and scaring may result. These last-mentioned entities may be seen as flattening of the esophageal wall up to circumferential strictures, not to be mistaken with a Schatzki ring which is located almost all the time at the GEJ and above a hernia. Patients with high risk of a Barrett esophagus, following even longer exposition of the esophageal mucosa to gastric acid, show strictures or ulcers in the middle

third of the esophagus and more reticular patterns of the mucosa. Prolonged inflammatory disease of the esophagus leads to fibrosis and longitudinal shortening of the esophagus, which is an important factor for the outcome of anti-reflux surgery and therefore has to be discerned and adequately reported [19]. All of these pathologies may be caused or at least accompanied by a hiatal hernia. For the visualization of a hiatal hernia, especially of sliding hernias, double-contrast examinations in different positions of the patient are mandatory. But it is important to know that the setting of the examination itself with distension of the esophagus and the pure act of swallowing lead to changes in the position of the GEJ relative to the diaphragm even in healthy individuals [24]. Hiatal hernias are categorized as followed:

- Type I: axial or sliding hernia. Displacement of the GEJ through the esophageal hiatus into the mediastinum. Most common type. Significant for GERD.
- Type II: true paraesophageal hernia. The GEJ remains in the physiological position and slipping of another part of the proximal stomach slips along the esophagus into the mediastinum.
- Type III: paraesophageal hernia with elements of type I and type II hernias.
- Type IV: large diaphragmatic defect with herniation of additional organs.

The significance of type II and IV hernias is more the relation to mechanical problems such as obstruction or ischemia then GERD. But the presence of a paraesophageal hernia may cause complication during anti-reflux surgery.

Therefore, functional imaging of the upper gastrointestinal tract with conventional imaging methods such as videofluoroscopy and double-contrast barium esophagram and functional MRI of the upper gastrointestinal tract contribute to a better outcome of anti-reflux surgery, even if not for the diagnosis of GERD.

5.3 Imaging After Anti-Reflux Surgery

During the early postoperative phase, an upper gastrointestinal series with water-soluble contrast media is, even though not undisputed [28], common sense in order for early detection of leakage, impaired esophageal emptying, and wrap or device migration [2, 18, 29]. Impaired esophageal emptying in the early period after surgery is most commonly only temporarily due to postoperative swelling. But with prolonged symptoms of dysphagia or impaired esophageal emptying, emesis, nausea, abdominal bloating, or again emerging symptoms of reflux further evaluation is necessary which can be done almost immediately using barium studies.

The most common type of anti-reflux surgery is the Nissen fundoplication, where the proximal part of the stomach is wrapped 360° around the esophagus. This wrap is often not visible in double-contrast barium studies but causes a typical “defect” of the gastric wall around the orifice of the esophagus (Fig. 5.1). If this wrap is to tight the esophagus is narrowed and the esophageal emptying is hindered (Fig. 5.2). If this wrap is to loose or incomplete and therefore of no functional use reflux will reoccur. Dysphagia or reoccurrence of reflux might be caused by wrap failure,

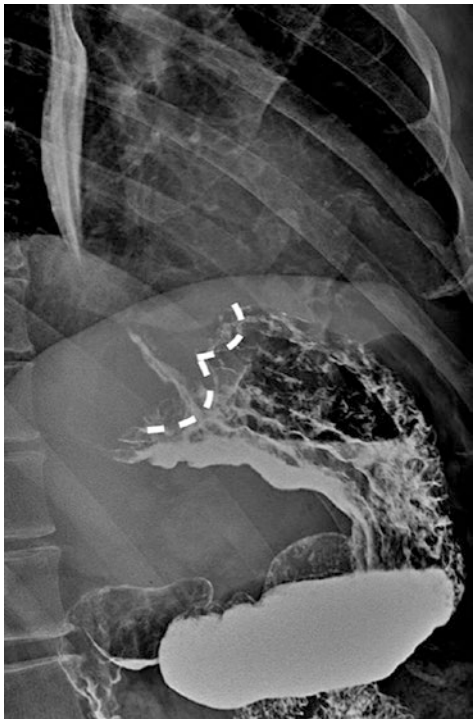

Fig. 5.1 Normal Nissen fundoplication. The not by itself visible fundoplication causes a typical lying "number three (3)"-shaped defect (dashed line) of the gastric outline with the esophagus nearly centered

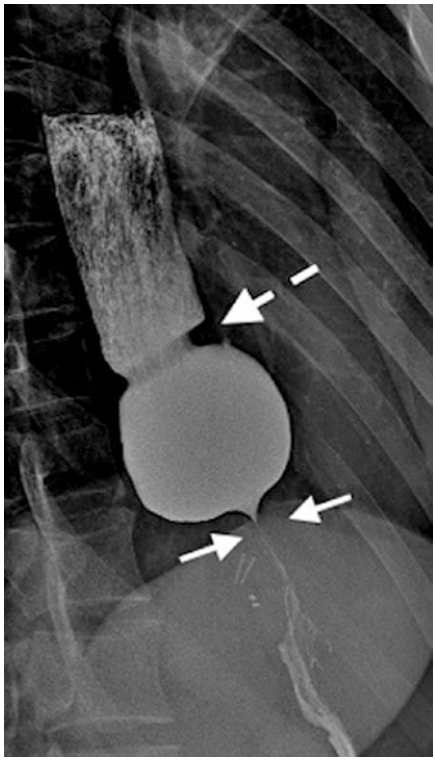

Fig. 5.2 Tight fundoplication with filiform lumen of the esophagus at the level of the fundoplication (small arrows). Dilatation of the supradiaphragmatic esophagus, which is filled with contrast media and food. Note the ring-like peptic stricture (dashed arrow)

which includes partial or total disruption of the wrap with or without reoccurrence of a hernia, slippage of the stomach, or the wrap, while the wrap is intact, above the level of the diaphragm (Figs. 5.3 and 5.4) and infradiaphragmatic slippage of the stomach through the intact and below the diaphragm lying wrap (Fig. 5.5).

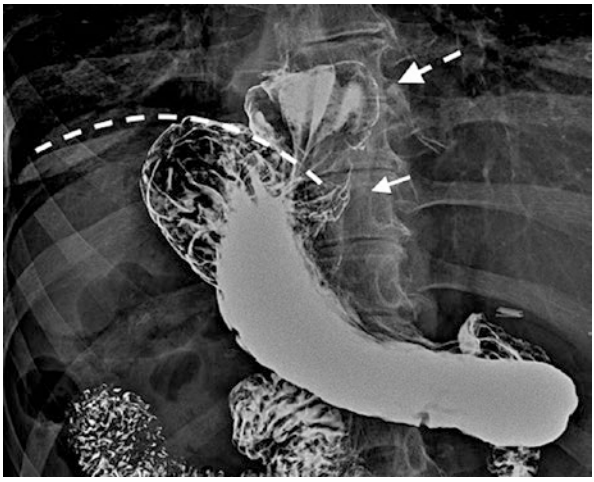

Fig. 5.3 Partially slipped stomach (dashed arrow) above the level of the diaphragm (dashed line). Note the infradiaphragmatic wrap, which in this case is partially visible (small arrow)

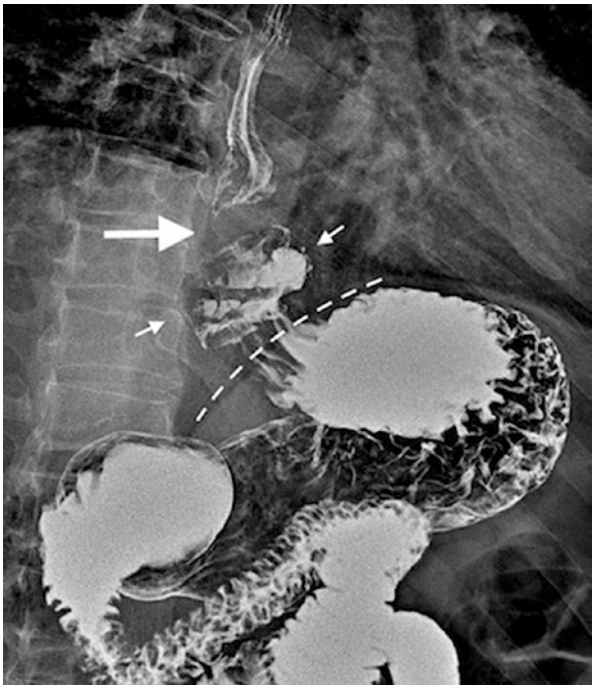

Fig. 5.4 Slippage of the intact wrap (bold arrow) together with a part of the proximal stomach (small arrows) above the level of the diaphragm (dashed line)

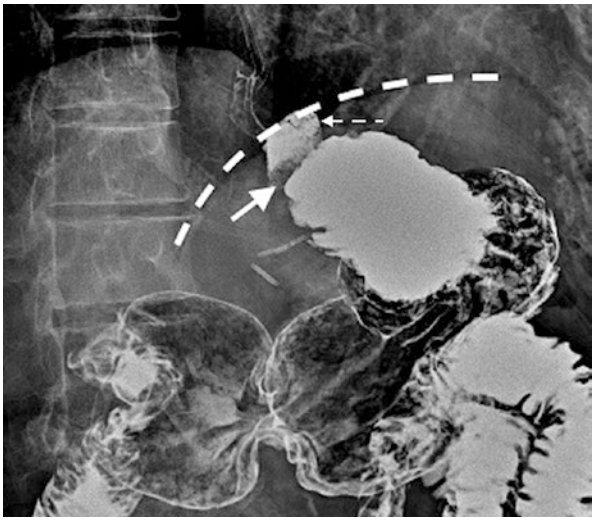

Fig. 5.5 Slippage of a part of the proximal stomach (dashed arrow) through the intact wrap (fat arrow) below the level of the diaphragm (dashed line)

These failures of the fundoplication may be categorized as followed [30]:

- Hinder Type 1: partial or complete disruption of the wrap with or without reoccurrence of a hernia.
- Hinder Type 2: slippage of a part of the stomach through the intact infradiaphragmatic wrap forming a supradiaphragmatic hernia.
- Hinder Type 3: slippage of a part of the stomach through the intact infradiaphragmatic wrap forming an infradiaphragmatic hernia.
- Hinder Type 4: supradiaphragmatic herniation of the wrap.

Another more and more common type of anti-reflux surgery is the usage of a magnetic sphincter augmentation device [31, 32]. The proper position of a magnetic sphincter augmentation device is around the esophagus at the GEJ (Fig. 5.6). During swallowing, the pressure of the physiological peristaltic wave overcomes the magnetic attraction of the device, thus leading to opening and passage of the bolus, which can be nicely imaged with double-contrast barium studies. The failures of this technique are not unsimilar to the failures of the Nissen fundoplication (Figs. 5.7 and 5.8), including the disruption of the device (Fig. 5.9).

All these complications of anti-reflux surgery may lead to the reoccurrence of GERD, which is shown with a failed lower esophageal sphincter electrical stimulation device (Fig. 5.10) [33, 34].

Imaging of the upper gastrointestinal tract with water-soluble contrast media and with barium is a well-documented, fast, readily available, and cost-effective method to evaluate early and late complications of anti-reflux surgery, with the restriction of using ionizing radiation. Functional MRI of the upper gastrointestinal tract is an promising accurate method in the evaluation of complications of anti-reflux surgery (Figs. 5.11, 5.12 and 5.13) with the advantage of not using ionizing radiation, but

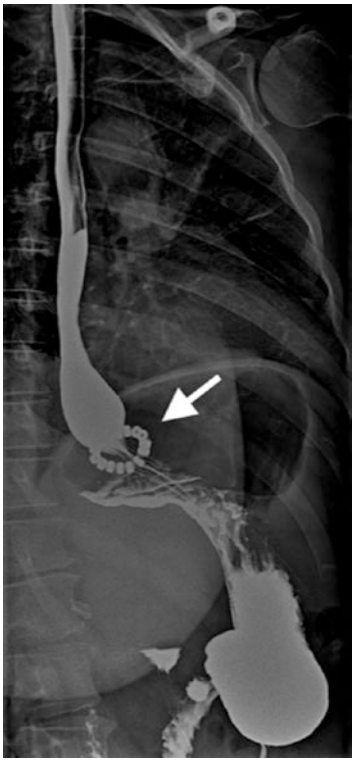

Fig. 5.6 Magnetic sphincter augmentation device in proper position (arrow)

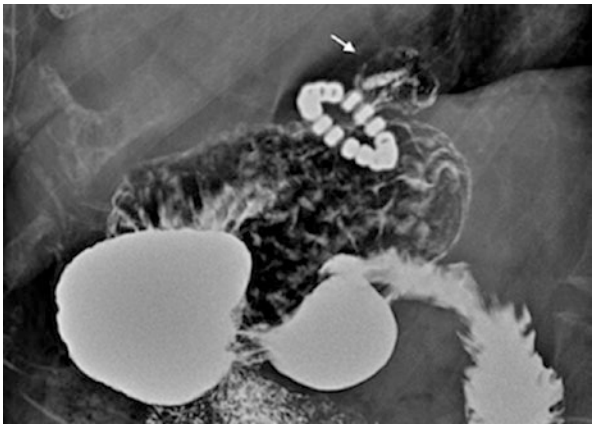

Fig. 5.7 Slippage of a small part of the proximal stomach (arrow) through a magnetic sphincter augmentation device, which is in proper position

the disadvantage of costs, availability, and the restricted usage after implantation of a magnetic sphincter augmentation device or lower esophageal sphincter electrical stimulation device. The LINX® magnetic sphincter augmentation device is conditionally safe for field strengths up to 1.5 Tesla, but as always with implanted devices, the manufactures' specification sheet or the individual implant pass has to be consulted.

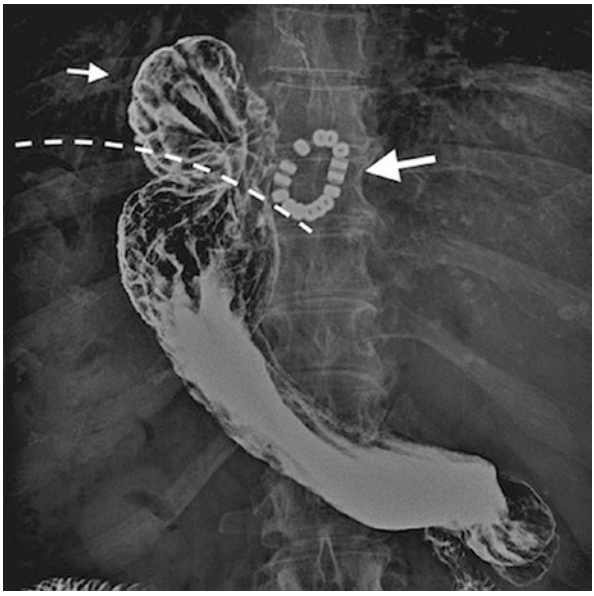

Fig. 5.8 Slippage of a magnetic sphincter augmentation device (bold arrow) above the level of the diaphragm (dashed line) together with a large portion of the proximal stomach in the form of a paraesophageal hernia (small arrow)

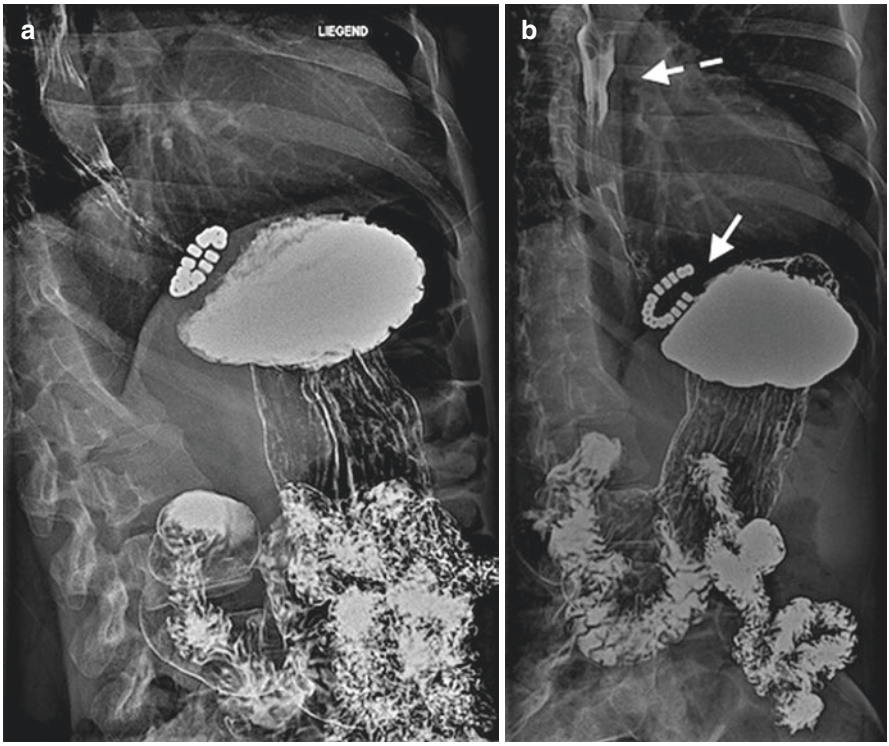

Fig. 5.9 (**a**) Patient 3 months after anti-reflux surgery with a fully operational magnetic sphincter augmentation device in regular position. (**b**) Same patient 12 months after anti-reflux surgery with a magnetic sphincter augmentation device. The device disrupted (arrow), resulting in reoccurrence of reflux (dashed arrow)

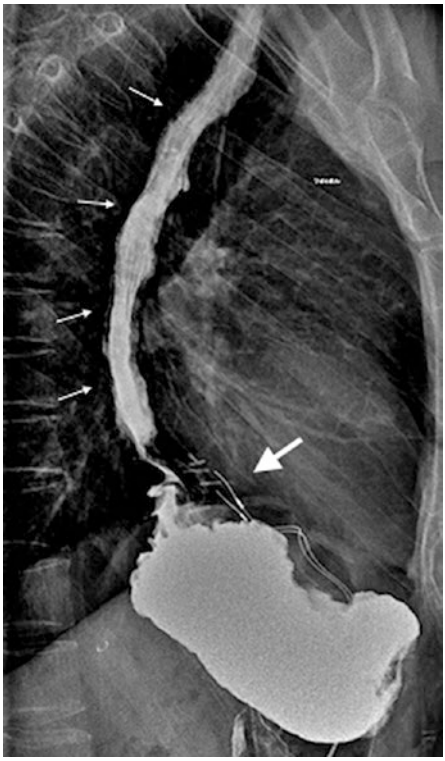

Fig. 5.10 Failure of a lower esophageal sphincter electrical stimulation device (bold arrow) leading to the reoccurrence of reflux (small arrows)

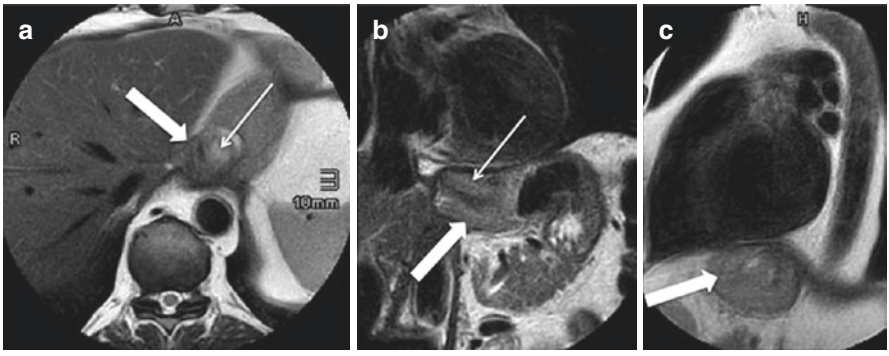

Fig. 5.11 Normal postoperative appearance after Nissen fundoplication on MRI. A ring-like "pseudotumor" (arrow) of the fundoplication acquired in the axial plane shows the Nissen fundoplication (**a**). The center of the "pseudotumor" (thin arrow) represents the esophagus. An additional coronal (**b**), and sagittal (**c**) view shows the correct position of the wrap under the diaphragm. (Images courtesy to C. Kulinna-Cosentini, MD, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna)

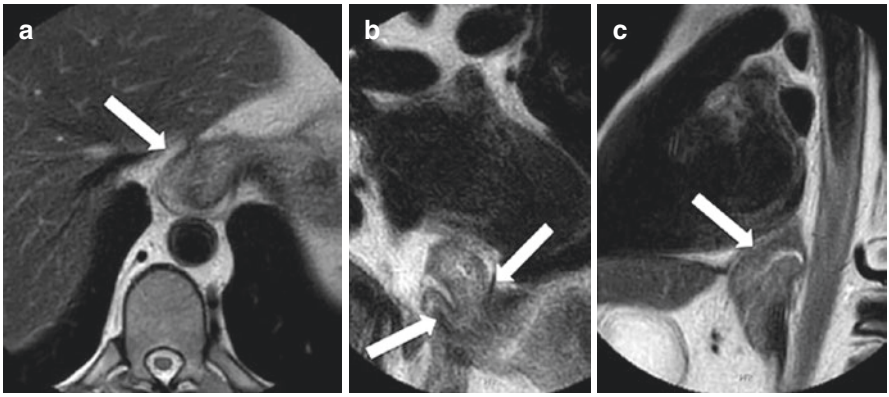

Fig. 5.12 Slipped wrap on MRI. T2w-HASTE sequences in the axial view were performed to demonstrate the integrity of the wrap (arrow) (**a**). MR fluoroscopy in the coronal (**b**) and sagittal (**c**) view shows that the entire wrap (arrow) lies above the esophageal hiatus in a patient with postprandial chest fullness. (Images courtesy to C. Kulinna-Cosentini, MD, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna)

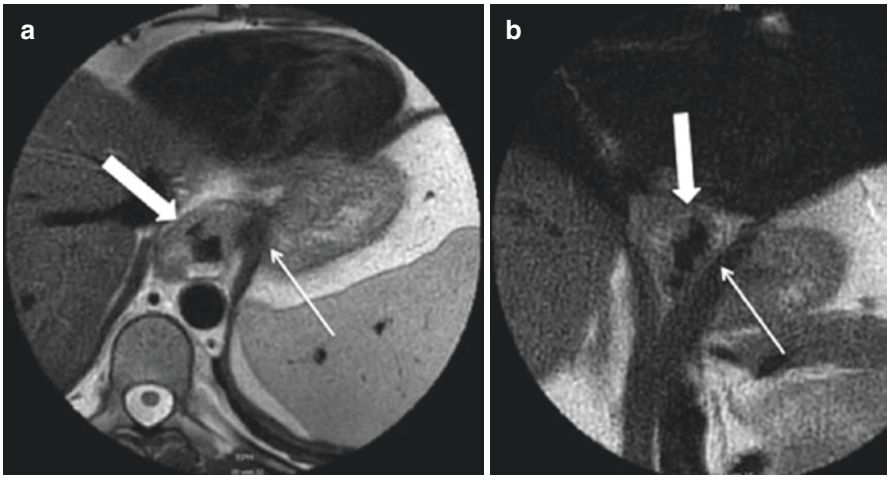

Fig. 5.13 Wrap rupture with recurrent hernia on MRI. Complete wrap disruption obtained in a patient with symptoms of recurrent reflux. The typical "pseudotumor" is missed on the axial (**a**) and coronal (**b**) view (thin arrows). A recurrent axial hernia is now demonstrated (thick arrows). (Images courtesy to C. Kulinna-Cosentini, MD, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna)

5.4 Conclusion

Although double-contrast barium studies and MRI of the upper gastrointestinal tract are, following the relevant guidelines, not necessary to establish the diagnosis of GERD, they are of great value in depicting and diagnosing complications and additional pathologies prior to anti-reflux surgery, such as swallowing disorders, shortened esophagus, esophageal dysmotility, eosinophilic esophagitis, hiatal hernias, and achalasia, and they are of great value in the diagnosis of early and late complications of anti-reflux surgery.

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Extraesophageal GERD and Management

6

Berit Schneider-Stickler

6.1 Etiology

Extraesophageal reflux (EER) manifestation has become a major pathophysiological problem with increasing clinical importance. EER can be either primary cause or major contributing factor to a variety of commonly occurring extraesophageal problems, if the reflux of stomach content causes troublesome symptoms and/or complications.

Increased attention to GERD has shifted focus to how and under which circumstances reflux influences physiologic processes in the upper airway beyond the esophagus [1].

As demonstrated in Table 6.1, extraesophageal reflux results in either direct reflux-associated symptoms due to direct contact between stomach content and mucosal structures or indirect vagal reflex responses elicited from the esophagus [2].

The clinical experience shows that symptoms mediated by EER are often nonspecific and overlap with those of other medical conditions.

As long as patients report on classic GERD symptoms (i.e., heartburn, epigastric regurgitation), EER is assumed to cause existing upper airway symptoms. Nevertheless, even in the absence of classic GERD symptoms, EER has to be

Table 6.1 Pathomechanism of extraesophageal reflux manifestations

Direct reflux-associated pathomechanism	Indirect reflex-associated pathomechanism
Direct reflux induced injury of the extraesophageal tissue (caused by contact with gastric acid)	Reflex responses elicited from the esophagus by the vagus nerve–mediated esophagobronchial reflex

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_6

considered and reviewed in all circumstances of any unspecific upper airways disorder. Patients with EER do not necessarily need to present classic GERD symptoms; rather, a large group of patients have "silent reflux" that can manifest in unspecific upper airway symptoms [3]. The percentage of patients with "silent" EER situation devoid of classic GERD symptoms is meanwhile estimated at about 20%.

However, the clinical situation is not clear in every patient, as organic lesions and reported symptoms do not always correlate. Thus, the exploration and diagnostics require a high degree of clinical experience and expertise.

On the one hand, patients with clinically "typical" reflux-associated organic lesions can be either symptomatic or asymptomatic concerning GERD. On the other hand, patients can report on severe EER symptoms without any detectable mucosal alteration in the extraesophageal region.

In patients with unspecific extraesophageal complaints, it is important to parse out the onset, duration, relieving factors, and exacerbating factors for the chief complaint in any patient even considering the gastroesophageal medical history [4]. Patients with extraesophageal GERD manifestations, when evaluated through upper digestive endoscopy, often present only a low prevalence of esophagitis [5].

The physiologic mechanism of extraesophageal/laryngopharyngeal reflux can be attributed to a breakdown of one or more of the four barriers to reflux:

1. Upper esophageal sphincter.
2. Lower esophageal sphincter.
3. Esophageal acid clearance.
4. Epithelial resistance.

If the barrier functions of lower and upper esophageal sphincters are not working properly, the direct mechanism of refluxate aspiration can trigger a tracheal or bronchial cough reflex. In case of a reflex-associated process, a vagally mediated bronchoconstriction can be found.

A further important risk factor for EER seems to be the excessive workload of the diaphragm in forced breathing task with special stress to the lower esophageal sphincter. Recent studies pointed out that GERD and EER have to be considered also as a work-related disease in selected professions. An increased intra-abdominal pressure seems to initiate GERD with extraesophageal manifestations more often, like in opera singers, wind players, and glassblowers [6–8].

The connection between GERD and certain diseases of the airway has been classified by the Montreal definition of GERD in 2006 [9, 10].

Considering this classification, there is agreement concerning both established and proposed associations with EER syndrome (see Table 6.2).

Usually general practitioners, pulmonologists, and ENT specialists are confronted with EER manifestations.

From the interdisciplinary point of view, extraesophageal symptoms can be divided into pulmonary and ENT symptoms (Table 6.3).

Table 6.2 Consensus on extraesophageal symptoms concerning the Montreal definition and classification (2006)

Established associations with EER	Proposed associations with EER
• Reflux cough syndrome • Reflux laryngitis syndrome • Reflux asthma syndrome • Reflux dental erosion syndrome	• Pharyngitis • Sinusitis • Idiopathic pulmonary fibrosis • Recurrent otitis media

Table 6.3 Extraesophageal symptoms associated with GERD classified regarding medical specialties modified after Richter [11]

Pulmonary manifestation	Manifestation in ENT
• Bronchial asthma • Chronic bronchitis • Chronic cough • Aspiration pneumonia • Apnea • Pulmonary fibrosis	• Chronic cough • Globus pharyngeus • Vocal cord granuloma • Reflux laryngitis • Loss of dental enamel and dental erosion • Chronic rhinosinusitis with/without polyposis nasi • Recurrent otitis media with effusion/chronic seromucotympanon

Given the increasing prevalence of GERD and its role in oropharyngeal, laryngeal, and pulmonary alterations, there is a growing need for better understanding of the underlying mechanism of pathophysiology.

It is important to diagnose and manage extraesophageal reflux symptoms appropriately. The interdisciplinary approach is not yet sufficiently established in daily practice and need to be intensified.

6.2 Pulmonary Extraesophageal Reflux Manifestation

Among pulmonary patients, special emphasis is given to the high percentage of GERD related cofactors to bronchial asthma, chronic bronchitis, and chronic cough [12, 13].

Asthma as an inflammatory lung disease with reversible airflow obstruction and bronchospasm causes episodes of wheezing, coughing, chest tightness, and shortness of breath. Etiologically, environmental factors like allergens or other aero irritants, genetic factors, side effects of medication, and viral/bacterial infection have to be taken into consideration as well as the direct or indirect impact by extraesophageal refluxate.

6.3 Chronic Cough

Chronic cough has a significant impact on the well-being of patients and stresses the healthcare services in many ways [14]. Cough is one of the most common conditions seen worldwide by primary care physicians and specialists.

Meanwhile, GERD has to be regarded as one the three most important etiologies of chronic cough. Afferent triggers are mediated by chemoreceptors and nociceptors within the respiratory system. They provide feedback to the cough center within the medulla, which, in turn, activates an efferent cascade and reflex that involves instantaneously the closure of the glottis. Tight laryngeal closure permits creation of an increasing subglottic pressure and a transglottic pressure gradient, which is the precondition for expectorating material from the respiratory tract when the subglottic pressure threshold is exceeded.

The traditional approach to chronic cough considers first of all smoking and regular medication with angiotensin-converting enzyme inhibitors. Meanwhile, the focus has extended to the diagnosis and management of other cough trigger components. Further classic triggers are aerogenic irritants/allergies, postnasal drip, respiratory infection, bronchial asthma, voice mis−/overuse, and other reactive airway diseases. These etiologies have to be excluded before suspecting that reflux may play a major role in developing chronic cough syndrome [14–16].

Chronic cough syndrome related to reflux is often considered a diagnosis of exclusion. In clinical practice, the evaluation of patients with chronic cough frequently involves trials of empiric therapy before initiating respective diagnostics. Patients are usually referred to further interdisciplinary examinations, if an empiric therapy trial could not solve the problem.

A common medical problem is the worsening of chronic cough symptoms by phonation in patients with underlying irritable larynx syndrome. The irritable larynx syndrome describes throat irritation that results from repeated vocal fold trauma by voice mis- and overuse. It can manifest as a sensory neuropathy during chronic cough [17, 18]. If the cough threshold is already decreased then voice use can lead easily to heavy coughing attacks.

Chronic cough can cause repeated trauma to the vocal fold tissue resulting in irritation and swelling of the vocal folds with a foreign body sensation in the larynx. This often requires a behavioral change of a person's reaction to this cough sensation and vocalization. A swallow of water might help to break the cycle and overcome the cough reflex.

6.4 Globus Pharyngeus

Globus pharyngeus (GP) is a symptom regularly reported by patients in ENT practice. It makes up to 4% of ear, nose, and throat (ENT) referrals and is reported to have been experienced by up to 45% of the population [19]. GP is usually multifactorial and cannot simply be reduced to a single hypothetical factor.

It describes the subjective feeling of a painless lump in the throat or an abnormal laryngopharyngeal sensation. Though there may not be an identifiable physical cause for the symptom [20], it is often associated with persistent clearing of the throat, chronic cough, hoarseness, and swallowing impairment.

It has been proposed that regurgitation of stomach acid and digestive enzymes in EER induces chronic inflammation of the laryngopharyngeal structures

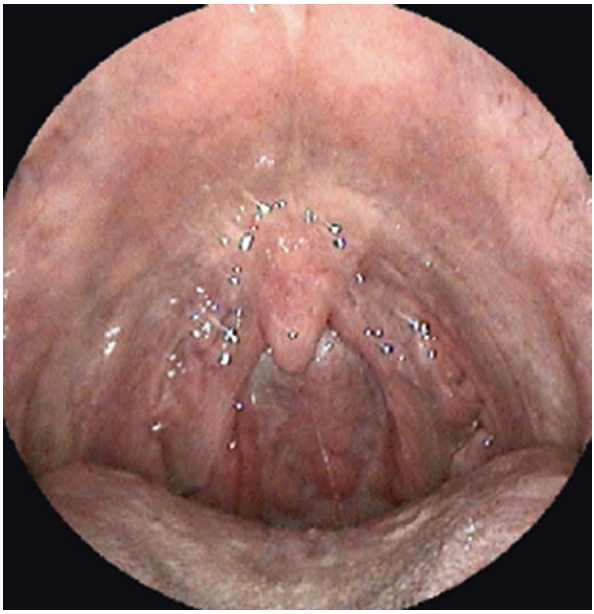

Fig. 6.1 Unspecific chronic lymphatic granulation of the pharyngeal mucosa in a GERD patient

resulting in unspecific inflammatory symptoms and GP symptoms [21]. Figure 6.1 shows a typical situation of unspecific chronic pharyngitis in a patient with suspected GP.

Anti-reflux treatment can often improve the clinical situation in GP, when EER plays a role on etiopathogenesis. EER is not the only reason for GP, but it can be contributing to the GP symptoms, as gastroesophageal reflux can be diagnosed in two-thirds of patients with GP [19]. However, the clinician should have in mind that EER can also be present in symptom-free controls without GP. Thus, GP is likely to be responsible for a subgroup of GP patients but cannot explain all GP cases [21].

6.5 Laryngopharyngeal Reflux Manifestation: Hoarseness, Vocal Fold Granuloma, and Benign Vocal Fold Alterations

Unspecific vocal and throat changes, which cannot be explained by other organic or functional voice disorders, indicate the possible influence of gastric or gastroduodenal reflux as a contributing or exacerbating factor, even in patients with no history of typical GERD. Laryngopharyngeal reflux manifestation is often associated with chronic cough syndrome and globus pharyngeus.

In 1991, Koufman operationalized laryngopharyngeal reflux [22]. A careful anamnesis and laryngostroboscopic examination can be enlightening. It can exclude laryngeal malignancy, benign vocal fold lesions, neurologic deficits, or phonation-associated vocal fold alterations.

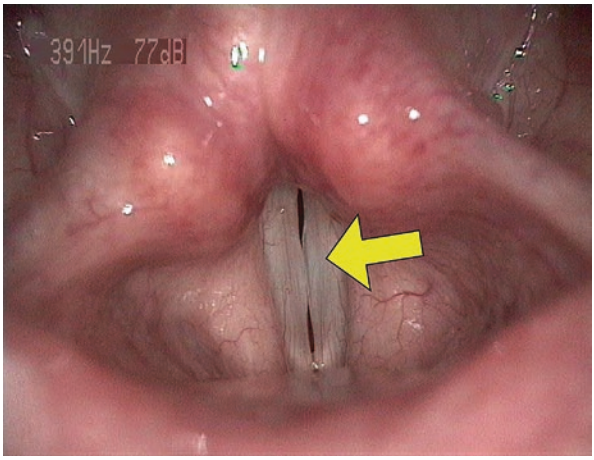

Fig. 6.2 Mild edema and swelling of the vocal fold edges in a female opera singer with GERD and phonation-associated vocal fold alterations

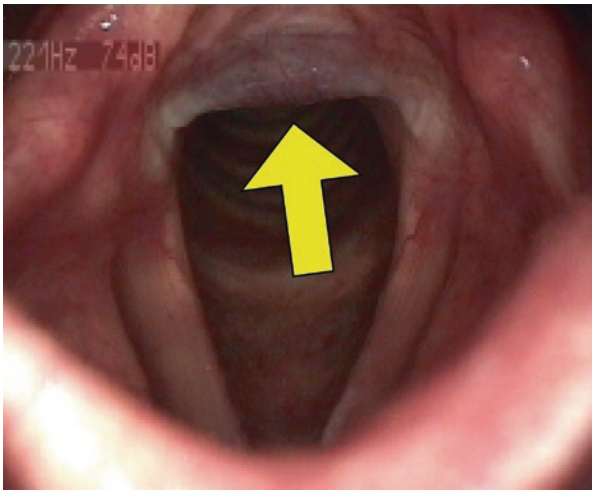

Fig. 6.3 Reflux laryngitis: posterior mucosal edema and thickening in the interarytenoid region

Typical laryngostroboscopic signs of reflux laryngitis are sulcus, pseudosulcus, thick secretions in the glottis, irregular free vocal fold edges (Fig. 6.2), erythema, interarytenoid mucosal edema (Fig. 6.3), posterior injuries such as ulcers and granuloma, and paradoxical movement of vocal.

Ulceration or granuloma in the cartilaginous part of the vocal fold has been strongly linked to reflux [23]. The mucosal damage by refluxate and the contact forces during phonation can cause either ulceration (contact ulceration) or granuloma (contact granuloma) as it is to be seen in Fig. 6.4. It is still difficult to determine the pathophysiologic relationship between reflux and granuloma [1].

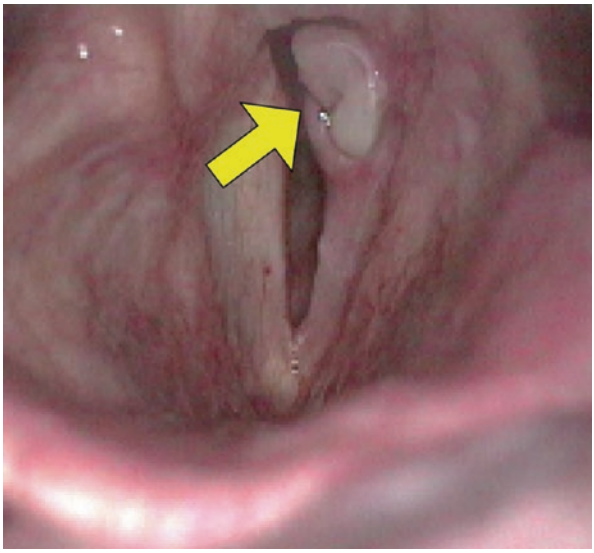

Fig. 6.4 Ulceration and granuloma in laryngopharyngeal reflux

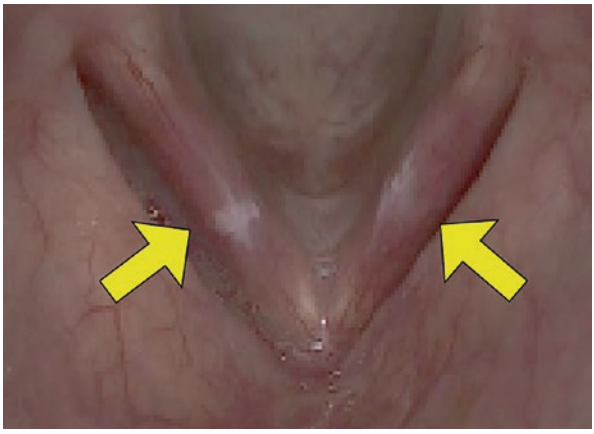

Fig. 6.5 Diffuse laryngitis with delayed wound healing

Meanwhile, laryngopharyngeal reflux has been associated with numerous other laryngeal alterations, including muscle tension dysphonia, Reinke's edema, laryngeal hyperirritability, laryngospasm, diffuse laryngitis, leukoplakia, glottic and subglottic stenosis, cricoarytenoid joint ankylosis, carcinoma, and other conditions [24, 25].

Many benign vocal fold lesions are of varying etiology and can be caused phonotraumatic secondary to voice overuse, misuse, or abuse. In situations without identifiable mass lesion or neurologic deficit, clinicians see a connection between vocal situation and reflux disease. EER is made responsible as a cofactor in many voice professionals and voice users, if the voice use alone cannot explain the development of the vocal situation. Reflux is believed to be a factor which negatively affects healing of vocal fold alterations after inflammation, phonotrauma, and also after laryngeal surgery (Fig. 6.5).

Table 6.4 Overview of patient-related outcome measures related to laryngopharyngeal reflux (modified after [1])

Study	Instrument	abbreviation
Wilson (1991)	Throat questionnaire	TQ
Deary (1995)	Glasgow-Edinburgh throat scale	GETS
Belafsky (2002)	Reflux symptom index	RSI
Carrau (2005)	Laryngopharyngeal reflux–health-related quality of life questionnaire	LPR-HRQL
Dauer (2006)	Supraesophageal reflux questionnaire	SERQ
Papakonstantinou (2009)	34-item Laryngopharyngeal reflux questionnaire	LPR-34
Andersson (2010)	Pharyngeal reflux symptom questionnaire	PRSQ

So far, patient symptoms have become a primary decision-driving method to identify those with LPR. Patient-reported outcome measures have become a principal diagnostic tool for LPR and monitoring the treatment outcomes [1, 4].

The most common patient-reported outcome measures related to laryngopharyngeal reflux have been summarized in Table 6.4.

The current controversies on LPR and GERD underline the problem of clinical interpretation of laryngostroboscopic findings as being reflux-related. Although clinical experience underlines the connection between LPR and EER, little success has been reached with correlation to investigations between specific laryngoscopic findings and the presence of reflux [26–28].

Regarding the need for further diagnostics, many colleagues argue that it is easier and more cost effective to treat laryngopharyngeal reflux empirically with a PPI than to spend additional time and effort investigating possible EER.

6.6 Vocal Cord Dysfunction

For the vocal cord dysfunction (VCD), several synonyms are in clinical use: paradoxical vocal fold movement (PVFM), paradoxical vocal fold movement disorder, and also induced laryngeal obstruction (ILO). VCD can be diagnosed already in children. Vocal cord dysfunction is a functional laryngeal dysfunction first described in the Nineteenth Century, as VCD causes paradoxical closing/adduction of vocal folds during inspiration, resulting in acute, episodic dyspnea. VCD is often mistaken for asthma, but is not responding to typical antiasthmatic treatment. Laryngoscopy during the acute respiratory event remains a gold standard for the diagnosis of vocal cord dysfunction. Exercise, psychological conditions, airborne irritants, rhinosinusitis, gastroesophageal reflux disease, or use of certain medications may trigger vocal cord dysfunction [29]. For many individuals, the role of postnasal drip and GERD in the pathogenesis of VCD is central, as they are often associated with VCD and likely lead to increased laryngopharyngeal sensitivity and hyperreactivity [30]. The patients need to be further examined in terms of the underlying pathogenesis of VCD. Management of VCD requires identification and treatment of underlying disorders. Treatment of acute episodes includes reassurance,

breathing instruction, and inhalation of a helium and oxygen mixture (heliox). Long-term management strategies include treatment for symptom triggers and speech therapy [29].

Usually, respiratory struggle during physical exertion (EILO = exercised induced laryngeal obstruction), asthma, and respiratory allergies have been suspected as underlying pathological factor. But refluxate of gastric contents can also induce laryngospasm and VCD. An interdisciplinary approach is needed to avoid unnecessary utilization of medical resources and potential delays of proper treatment [31]. In patients with suspected VCD, a gastroenterological examination including gastroscopy is strongly recommended.

6.7 Dental Erosions

Dental erosion can be considered as an extraesophageal manifestation of gastroesophageal reflux disease [9, 32, 33]. The association between acid reflux and dental erosion was first described by Howden in 1971 and was later confirmed in other studies. As dental erosion occur more often in patients with GERD, and subjects with unexplained dental erosions should be referred to gastroenterologists for further diagnostics.

Dental erosions are defined as a physical result of pathological, chronic, localized, painless loss of dental hard tissue, and the outer surface is chemically destroyed by acid or chelates [34]. Dental erosions are usually of multifactorial etiology. Even the interaction of all etiologic factors may cause a synergistic effect. According to the depth of the lesions, they might be divided into surface and deep ones, according to the localization into generalized and localized ones and according to pathogenic activities into manifesting and latent ones.

The connection between GERD and erosive changes on teeth is not absolute because not everyone with a diagnosed GERD presents also erosive teeth changes. GERD may be a risk factor for dental erosions only if it is in combination with refluxate regurgitation.

Further reasons for dental erosions might be attrition, abrasion, and abfraction [34]:

- *Attrition* is a defect of both dental tissue and restoration and is caused by tooth-to-tooth contact during mastication or para-functioning. Occlusal surfaces are smooth, shiny, evened, and hard and on amalgam fillings facets are observable. The bottom of the defect may be located both in enamel and in dentine [35].
- *Abrasions* occur with direct contact between the tooth and an external substance (tooth whitening paste, anti-nicotine, soda). Dental abrasion is most commonly seen at the cervical necks of teeth, but can occur in any area, even interdentally from vigorous and incorrect use of dental floss. Acid erosion has been implicated in the initiation and progress of the cervical lesion, while toothbrush abrasion has long been held as the prime cause of cervical abrasion [36].

- *Abfraction* is a defect which is characterized by loss of dental tissue in the cervical region. It is caused by compression and stretching forces which take place during dental flexure. At inadequate occlusal relation, the changes are localized mainly vestibular and they are of a wedged shape [37].

Dental erosion can result in tooth sensitivity, poor esthetic appearance, loss of occlusal vertical dimension, and functional problems. Clinicians must have thorough understanding of the causes of dental erosion as identification of the cause is the first step in its management. The inspection of the oral cavity in search for dental erosion should become a routine maneuver in patients with GERD [34].

6.8 Postnasal Drainage

Daily, the human body produces between 0.75 and 1.5 L of secretions from the upper airway, which has to be swallowed into the esophagus [38]. Thus, postnasal drainage is not a syndrome [39], but has to be considered as a rather normal physiologic process.

Clinical experience is that patients describing postnasal drip/drainage often complain on significantly thickened secretions, which the body recognizes as abnormal, thus manifesting in frequent throat clearing and cough.

Patients with globus sensation, postnasal drainage, or cough traditionally are first of all thought to be allergic. Thus, they are initially treated with antihistamines, decongestants, and cough protecting drops. All of these interventions usually increase the viscosity of the secretion and can exacerbate symptoms.

Therefore, hydration and avoidance of any drying medications can improve the symptoms.

Nevertheless, in patients with therapy resistant and persistent postnasal drainage symptoms, also extraesophageal symptom manifestation has to be considered.

6.9 Chronic Rhinosinusitis (CRS) With and Without Nasal Polyposis

The prevalence of chronic rhinitis is estimated to be high as 30% of the total population [40].

Chronic rhinosinusitis (CRS) is defined as an inflammatory disorder of the nose and the paranasal sinuses lasting for at least 12 weeks.

According to the EPOS 2012, it is characterized by the following clinical features [41]:

- nasal blockage/congestion/obstruction and/or,
- rhinorrhea: nasal discharge, anteriorly or posteriorly,
- ± facial pain/pressure
- ± reduction/loss of smell.

and either endoscopic signs of:

- polyps and/or,
- mucopurulent discharge and/or edema primarily in the middle meatus and/or,
- changes within the ostiomeatal complex and/or sinuses on computer tomography.

It affects approximately 15% of the adult population and may be divided into three clinical subtypes [42]:

- CRS without nasal polyps (CRSsNP) in Fig. 6.6,
- CRS with nasal polyps (CRScNP) in Fig. 6.7, and
- allergic fungal rhinosinusitis (AFRS).

Allergic rhinitis is considered as the most common etiology and is a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose [43]. Over the past decade, extraesophageal reflux has been hypothesized to be one of the possible factors of the nonallergic rhinitis with nasal hyperreactivity that contributes to the development and worsening of chronic rhinosinusitis (CRS). GERD has to be excluded in any nonallergic, noninfectious chronic rhinitis. Otherwise, the treatment outcome might be poor.

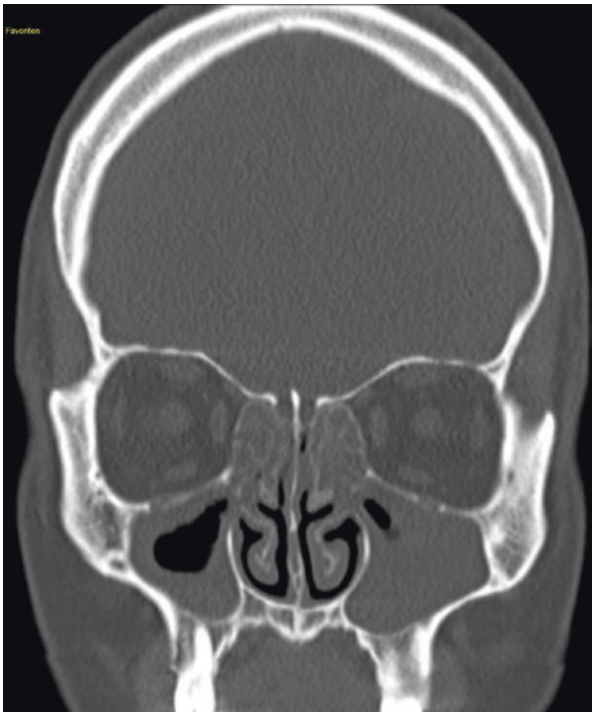

Fig. 6.6 Computer tomographic image of a patient with chronic rhinosinusitis due to GERD

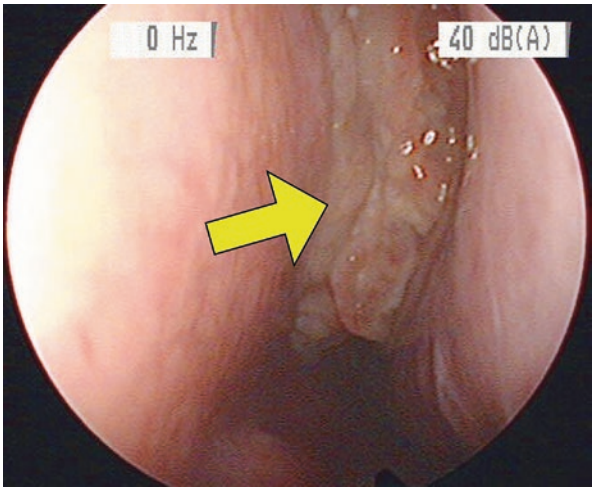

Fig. 6.7 Polyposis nasi during rigid anterior rhinoscopy

From the pathophysiologic point of view, two potential mechanisms are considered in order to explain how GERD and CRS may interact: direct cytotoxic effect of gastric refluxate displaced to the nasal cavity or an indirect mechanism due to a reflex from esophagus to the sinuses via the autonomic nervous system [44]. Several studies have tried to identify reflux or reflux components in the nasal cavity. As to acid, it has so far not been possible to document an increased incidence in patients with CRS compared to controls [44, 45], but in a small group of medically refractory CRS, most patients had a positive pharyngeal pH probe.

In other studies, patients with recurrent CRS had significantly more reflux events in the esophagus, but did not show more direct extraesophageal reflux signs [46].

However, pepsin could be found regularly in nasal lavage in patients with CRS [47]. Another ongoing discussion on direct reflux-associated association considers the evidence of *Helicobacter pylori* in the nasal and paranasal cavities. The bacterium was detected in the mucosa from ethmoid cells in many patients with CRS in comparison to controls [48]. But it seems to be present not only in patients with CRS but also in control subjects in the same percentage [49].

When it comes to an indirect GERD manifestation, as the underlying pathophysiological mechanism of CRS, it is believed that this can be an analogue of the reflex between gastroesophageal reflux and bronchial constriction [50]. Wong made an acid infusion test by installing saline and acid in the esophagus and measured an increased nasal mucus production. However, the number of participants in this study was low, and the result was not statistically significant.

6.10 Otitis Media

Acute otitis media (AOM) and chronic otitis media with effusion (OME) are among the most frequent causes for visits to the doctor especially in children in the age of 1 to 3 years [51]. There are several well-known conditions that cause or facilitate the

development of middle ear infections. The most important etiologic factors seem to be upper respiratory infections (including bacterial infections), anatomical characteristics, an immature immune system, allergies, and enlarged adenoids [52]. The acute otitis media with purulent effusion (AOM) is predominantly caused be single microorganism, most commonly *Haemophilus influenzae*, and also *Streptococcus pneumoniae*, *Alloiococcus otitidis*, or *Moraxella catarrhalis*, whereas otitis media with non-purulent effusions (chronic seromucotympanon) seems to be caused by predominantly polymicrobial entities and nonbacterial agents [53].

Enlarged adenoids are considered as the main reasons for chronic dysfunction of the Eustachian tube resulting in otitis media with effusion in younger children. Usually it can be treated successfully with adenoidectomy and paracentesis. In few children, the symptom of middle ear effusion reoccurs after adenoidectomy.

Here in consequence, it is necessary to identify other possible risk factors. Extraesophageal reflux is considered as one contributing risk factors of OME.

Extraesophageal reflux can cause inflammatory changes in the Eustachian tube and middle ear, with consequential development of middle ear inflammation [51]. Twenty-four–hour monitoring of oropharyngeal pH and detection of pepsin in the middle ear fluid are suitable methods for detecting EER in children with OME.

Otitis media with effusion occurs frequently in younger children with resulting conductive hearing loss. This is one of the important causes of hearing loss, which can lead to profound effects on language skills and cognitive development of children.

Pepsin and pepsinogen in otitis media with effusion are predominantly caused by LPR and should be considered as LPR predictors [54, 55].

6.11 Diagnostics and Management

Patients with extraesophageal reflux symptoms may require an individual antireflux treatment and/or referral to a gastroenterologist for further appropriate diagnostics.

Diagnosis of extraesophageal reflux manifestation has traditionally relied on symptomatology, questionnaires, laryngoscopy, stroboscopy, endoscopy, pH-monitoring, and radiologic examinations including barium swallow.

Combined multichannel intraluminal impedance and pH-monitoring provide an advance in EER/LPR diagnostics.

The Peptest, an immunoassay used to detect pepsin, can be used to diagnose extraesophageal reflux, especially in children with chronic otitis media with effusion [51].

First-line therapy for patients with extraesophageal reflux symptoms are lifestyle changes. Certain foods, body position, smoking, alcohol, and obesity should be considered in the GERD treatment.

Current guidelines for extraesophageal reflux manifestation suggest an initial empiric trial of proton pump inhibitors for at least 3 months in patients with suspected GERD symptoms. For those patients who improve with PPIs, GERD is

presumed to be the etiology. In patients with refractory reflux and failure to respond to a 3-month trail of behavioral changer and gastric suppression by adequate doses of PPI, combined multichannel impedance/pH monitoring might provide the single best strategy for evaluating reflux symptoms [56].

Nevertheless, the treatment of any extraesophageal manifestation has to consider not only the antacid medication (PPI) but also the surgical intervention, lifestyle changes/diet, voice therapy, antiallergic co-medication, and any other disorder-related treatment.

Acknowledgments Between manuscript design and printer's layout, part of the content of this paper has been already published in the Hamdan Medical Journal [57].

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Anti-Reflux Surgery I: Fundoplications

7

Marc A. Ward and Lee L. Swanstrom

7.1 Introduction

The prevalence of gastroesophageal reflux disease (GERD) continues to increase and is now one of the most commonly treated chronic diseases of the abdomen [1]. This increasing incidence appears to correlate with the rising incidence of obesity worldwide. Most GERD patients present with typical symptoms (i.e., regurgitation and heartburn), yet rarely undergo a complete diagnostic evaluation. They are most often managed with nonsurgical therapy such as proton pump inhibitors (PPI) [2]. Nonresponders to PPI therapy or patients who exhibit atypical symptoms (i.e., extragastrointestinal manifestations including cough, asthma, laryngitis, and chest pain) require further workup, which at the very least includes esophagogastroduodenoscopy (EGD) and esophageal pH monitoring [3]. Adequate evaluation of all patients with long-standing GERD is crucial since complications of GERD may cause significant morbidity in the form of esophagitis, peptic stricture formation, Barrett's esophagus, and even adenocarcinoma.

Studies comparing the medical management of GERD to surgical alternatives have demonstrated that anti-reflux operations result in significantly less esophageal

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_7

acid exposure and increased LES pressure compared to medical treatment alone. According to the guidelines written by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), surgical procedures successfully cure GERD 85–93% of the time [4]. The most frequent indications for anti-reflux operations are symptoms that are refractory to pharmacological therapy [5]. Other indications include a reluctance to take lifelong PPI therapy, extraesophageal manifestations of GERD, and objective documentation of reflux via esophageal pH monitoring, impedance, or endoscopic findings while on pharmacotherapy. It is crucial that patients who undergo surgery for GERD have adequate esophageal motility to overcome the newly created resistance as a result of the surgical procedure. Therefore, we recommend high-resolution manometry be obtained in all patients before proceeding with an operation. Twenty-four-hour pH testing is critical for patients with atypical symptoms and useful for all patients to verify and quantify the reflux which subsequently serves as a baseline for follow-up.

GERD is a multifactorial disease, and clinical presentations among patients can differ dramatically. Several studies have demonstrated that the following factors may predict successful surgical outcomes in GERD patients undergoing anti-reflux surgery:

- Positive responders to anti-reflux medications [6, 7].
- Patients who present with typical symptoms [7–10].
- The presence of objective evidence of GERD demonstrated on upper endoscopy or esophageal pH study [11, 12].
- Those without previous anti-reflux surgery [13, 14].

There are few absolute contraindications to the surgical treatment of GERD with the exception of esophageal cancer or Barrett's mucosa with high-grade dysplasia. The presence of low-grade dysplasia, however, is not a contraindication for acid-reducing surgery. In a study by Hofstetter et al., patients with Barrett's esophagus that included low-grade dysplasia underwent anti-reflux surgery. Seventy-nine percent of patients had complete resolution of their symptoms, and in 7 of 16 patients (44%), low-grade dysplasia regressed to non-dysplastic Barrett's. Both high-grade dysplasia and adenocarcinoma were successfully prevented in all 97 patients included in the study [15]. The use of fundoplications in anti-reflux surgery is highly effective at symptoms resolution as well as the prevention of disease progression.

It should be noted that fundoplication can be associated with side effects and potential complications, and this should be taken into consideration when offering it to patients. While surgery-related mortality is extremely rare (<1:500), perioperative complications such as bleeding, perforation, infection can happen in 5–10% of cases, particularly in low-volume practices. In addition, the majority of patients will have side effects related to the fundoplication. These include dysphagia, early satiety, bloating, and flatulence [16]. While usually temporary, these symptoms can be troublesome for weeks to months and on rare occasions more persistent and occasionally require intervention.

7.2 Laparoscopic Versus Open Technique

In the modern era, the laparoscopic transabdominal approach is preferred in the majority of patients undergoing anti-reflux surgery. In most cases, a transthoracic approach is only performed when revisional surgery via the abdomen is difficult [17]. When looking at all fundoplications, there have been more than ten randomized control trials that show a significant patient benefit with laparoscopy. Patients who undergo a laparoscopic approach are discharged from the hospital 2.5 days earlier, return to their normal activities 8 days earlier, and have a 65% reduction in the odds of a postoperative complication [18, 19]. Laparoscopy provides improved angle for visualization in addition to magnification that makes visualization of the hiatus during fundoplications better. In a 10-year randomized controlled trial comparing laparoscopic and open Nissen fundoplication, it was shown that the open group had twice the number of reoperations as well as a higher incisional hernia rate. In addition, both groups showed similar rates of symptom resolution, postoperative PPI use, quality of life, and objective reflux control [20]. This confirmed that the laparoscopic approach for fundoplication is currently the gold standard for the surgical management of GERD.

7.3 Total Fundoplication

Rudolf Nissen fortuitously discovered the 360° or total fundoplication while performing a partial esophagectomy in 1956. After completing the operation, he wrapped the gastric fundus around his anastomosis as a way to prevent anastomotic leak. Subsequently, he realized that this method prevented reflux, and surgeons have been using a variation of the Nissen or total fundoplication as an anti-reflux operation ever since [21].

Originally, Nissen described a long wrap of the gastric fundus around the lower esophageal sphincter. Since his original description, modifications have been made to optimize the efficacy of the surgery. Surgeons have learned through experience and empiric evidence that it is important for a total fundoplication to not be too long or too tight. A short "floppy" total fundoplication has been shown to not only relieve symptoms of reflux but also decrease the incidence of postoperative side effects such as dysphagia and bloating [22, 23]. Surgeon experience and hospital volume have also been shown to improve outcomes of the operation in both the short and long term [24].

The goals of a total fundoplication (TF) are to restore the reflux barrier at the gastroesophageal junction (GEJ) without causing distal obstruction of the esophagus. The 360° wrap around the GEJ leads to an increase in the resting pressure, while not impairing the relaxation of the LES, thereby preventing reflux of gastric contents into the esophagus [25, 26]. In addition, the wrap decreases compliance of the gastric cardia, which reduces the frequency of transient LES relaxations [27]. If this surgery is performed correctly, a new valve can be identified upon retroflexion with the endoscope as seen in Fig. 7.1.

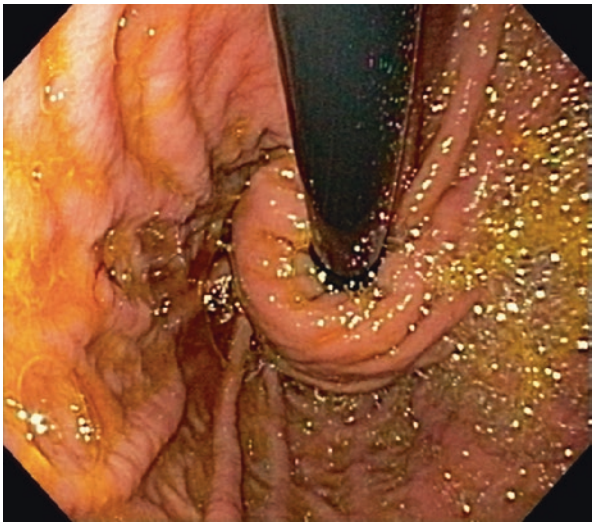

Fig. 7.1 Endoscopic view of stomach following completion of a total fundoplication

Greater than 80% of individuals who undergo a TF experience have no adverse long-term symptoms postoperatively [28]. Impaired swallowing (dysphagia), early satiety, and gas-related symptoms caused by an inability to release air from the stomach (gas bloat) are the most common adverse symptoms experienced immediately in the postoperative period [29]. Rarely will either of these early symptoms require intervention. If, however, symptoms of dysphagia persist beyond 6 weeks or gas bloat beyond 6 months, endoscopic dilation of the GEJ may offer symptomatic relief [30].

Although a TF involves a 360° wrap of the gastric fundus around the esophagus, there are two popular variations in technique that are employed to achieve sufficient symptom resolution. The first is based on the original work of Nissen, where he describes his surgical method more like an invagination of the distal esophagus into the gastric fundus. In this technique, often referred to as the anterior-posterior wrap, the location of the greater curvature is maintained at the 3 o'clock position, while the anterior and posterior walls of the fundus are pulled together to the 9 o'clock position around the GEJ. The other technique often referred to the greater curvature wrap involves grasping the greater curvature of the fundus, pulling it behind the esophagus and attaching it to the fundus that is located on the patient's left side. Graphical representations of the different construction methods for a total fundoplication are shown in Fig. 7.2. The final appearance of the wrap appears similar regardless of the technique employed and can be seen in Fig. 7.3.

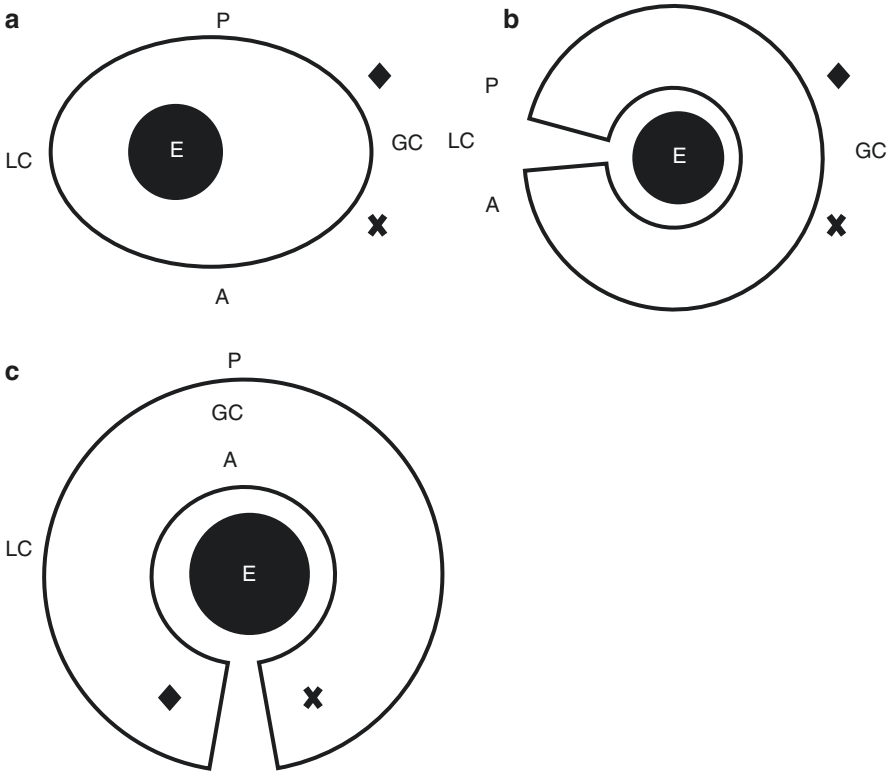

Fig. 7.2 Variations of Nissen creation. (**a**) Normal anatomy, (**b**) anterior-posterior wrap, (**c**) greater curvature wrap. *E* esophagus, *A* anterior stomach, *P* posterior stomach, *LC* lesser curvature, *GC* greater curvature, *Diamond* greater curvature near angle of His, *X* greater curvature 6–7 cm from angle of His

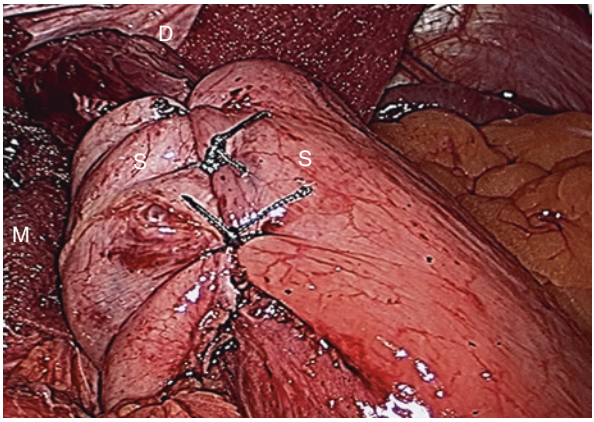

Fig. 7.3 Laparoscopic view of completed total fundoplication. *S* each side of the stomach wrapped around the lower esophageal sphincter, *D* diaphragm, *M* biologic mesh used in diaphragmatic hiatal closure

7.4 Posterior Partial Fundoplication

A 360° total fundoplication is the most frequent anti-reflux surgery performed worldwide. However, this procedure can lead to side effects, such as bloating, dysphagia, and increased flatulence which can be particularly troublesome to patients with mild symptoms or already predisposed to the same. Partial fundoplications have been proposed in an effort to reduce these postoperative symptoms while preserving good reflux control.

In 1963, Andre Toupet, a French surgeon, began experimenting with the idea of a partial fundoplication due to the development of dysphagia in some of his patients following a total fundoplication. He later published his technique of a posterior 180° partial fundoplication [31]. Modifications to his original technique, including increasing the degree of the fundic wrap and closure of the hiatal opening have been adapted since his original description. Today, the 270° posterior partial fundoplication is commonly referred to as a Toupet fundoplication. Shown in Fig. 7.4 is what a constructed Toupet fundoplication appears at completion. The fundus of the stomach is attached to either side of the esophagus as well as the hiatus.

The partial posterior fundoplication has been shown to be effective at reducing reflux and improving quality of life. A study by Kamolz et al., compared Nissen and Toupet and showed that only 10% of patients experienced symptoms following the Toupet at 10 years from the operation. Other studies have shown successful control of symptoms in the vast majority of patients even two decades from the operation [32]. The surgery itself tends to be well tolerated with <5% of patients experiencing early complications including pneumothorax, wrap herniation, perforation, hemorrhage, wound infection, or mortality. In fact, 85% percent of patients who underwent a partial posterior fundoplication report that they are glad they had the surgery or would recommend it to a friend [33].

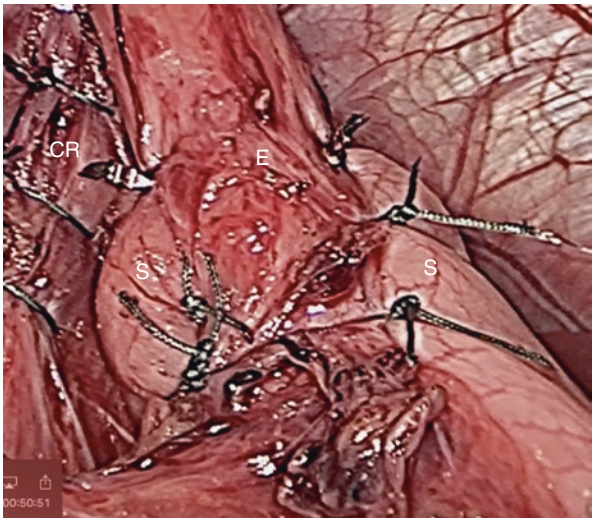

Fig. 7.4 Laparoscopic view of completed 270° posterior partial fundoplication. *S* stomach, *E* esophagus, *CR* crural repair

Early studies comparing TF and PPF demonstrate that TF was superior in relieving heartburn, improving quality of life, and reducing PPI use postoperatively [34, 35]. However, in a recent trial by Shaw et al., 100 patients were randomized to either a TF or PPF. No differences were seen in the incidence of dysphagia, GERD symptom relief, or quality of life at an average of 55 months between the two groups [36]. Other randomized control trials have confirmed that postoperative quality of life and reflux resolution are similar between the two groups, yet patients with a PPF have a lower incidence of postoperative dysphagia and gas bloat [37, 38]. Given the high number of randomized controlled trials comparing these two operations, independent meta-analyses have been conducted and concluded that both groups have similar rates of reoperation rates, dysphagia, gas-related symptoms, and reflux control [39, 40]. As a result, it appears PPF is a viable alternative to TF with a possible reduction in postoperative dysphagia. While some use PPF preferentially, many use it for patients with dysphagia and poor esophageal motility.

7.5 Anterior Partial Fundoplications (AF)

Anterior fundoplications (AF) tend to have the lowest side effect profile compared to TF and PPF. Ten-year data suggests that outcomes related to control of GERD can be good, and many patients have similar patient satisfaction to overall outcomes as those who undergo a PPF or TF [41]. For this reason, an anterior fundoplication is most often used in patients who may be at an increased risk to develop negative side effects postoperatively. Patients who suffer from reflux, and also have problems with esophageal motility, frequent aspirations or throat symptoms, or coexisting complicated medical conditions, may benefit most from this operation.

Historically, anterior fundoplications were performed selectively in patients due to a lack of long-term outcome data. Multiple randomized control trials have since been completed to determine the effectiveness of a 180° (Dor) AF compared to TF. In a study by Baigrie et al., 2-year outcomes of 161 patients showed equivalent outcomes between AF and TF in terms of reflux control, but less dysphagia in the AF group. However, patients who underwent AF also had a higher incidence of reoperation for recurrent reflux than those who had a TF [42]. In another trial by Cao et al., 5-year outcomes making the same comparison demonstrated equal reflux control in both groups with less flatulence in the AF group [43]. Unlike these two studies, other trials have compared a 90° AF, which demonstrated fewer side effects, but was also associated with a higher incidence of reflux [44, 45]. For this reason, a 180° AF is the preferred anterior fundoplication performed today (Fig. 7.5).

Overall, although data from these trials demonstrate that AF can provide early reflux control, while minimizing postoperative side effects, this reduced side effect profile appears to come with a higher risk of recurrent reflux. Therefore, the anterior fundoplication is primarily used to prevent reflux after myotomy or in complex patients with extremely poor motility. Table 7.1 summarizes the advantages and disadvantages of the most commonly performed fundoplications.

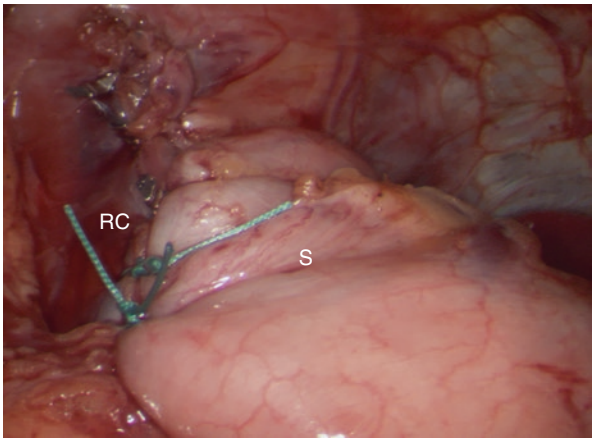

Fig. 7.5 Laparoscopic view of completed 180° anterior partial fundoplication. *S* stomach, *RC* right crus

Table 7.1 Advantages and disadvantages of major fundoplications

	Advantages	Disadvantages
360° Total fundoplication	Very effective long-term control of reflux	Increased flatulence, bloating, and dysphagia
270° posterior partial fundoplication	Less postoperative dysphagia	Length of wrap determines quality of reflux control and can vary
180° anterior partial fundoplication	Less postoperative dysphagia	Recurrent symptoms over time

7.6 Anterior Versus Posterior Fundoplication

Comparisons between AF and PPF have also been subjected to randomized control trials to determine whether differences in postoperative morbidity and reflux symptom control exists. In a single institution, study by Hagedorn et al., nearly 100 patients were randomized to either a PPF or AF. At 1 year, the patients in the PPF groups had better control of typical reflux symptoms and also had a higher percentage of patients who suffered from dysphagia [46]. A similarly constructed study by Engstrom et al., showed that PPF maintained better control of reflux symptoms and decreased reoperation rates without increased rates of dysphagia at 5 years from the operation [47]. To get more clarification on this matter, a systematic review and meta-analysis was performed comparing AF and PPF. This review found that PPF is associated with increased reflux symptom relief as well as decreased reoperation rates when compared to AF. Short-term dysphagia rates were less in those who receive anterior wrap; however, this benefit is not seen as patients get farther and farther from surgery. The authors of this review conclude that of these two, PPF is a better of choice for GERD [48]. Despite these multiple randomized controlled trials and meta analyses, controversy still exists as to which fundoplication is the most effective at controlling symptoms with a lowest side effect profile. In the United States, the most common fundoplication is the TF, while partial fundoplications remain more popular in Europe.

7.7 Special Circumstances

7.7.1 GERD in the Morbidly Obese

Obesity and the development of GERD are related. This is a linear association, as the prevalence of GERD increases with increasing body mass index (BMI). Some studies have indicated that morbidly obese patients have a higher rate of failure compared to their nonobese counterparts [6]. Lifestyle modification and weight loss are often initial measures recommended by physicians to patients who suffer from GERD. This is supported by the fact that people who lose weight following Roux-en-Y gastric bypass (RYGB) frequently have improvement in their reflux symptoms [49]. Between 75 and 95% of patients obtain resolution of reflux symptoms following RYGB within 1 year of the operation [50]. Because of this high success rate, coupled by the resolution of other obesity-related comorbidities, RYGB is the procedure of choice for morbidly obese patients who suffer from GERD.

7.7.2 Failed Fundoplications and Revisional Surgery

Recent 20-year follow-up data shows that fundoplication provides a robust and durable treatment for more than 80% of GERD patients [51]. The generally accepted range for failure following fundoplication is 3–16% [52]. However, not every patient who suffers from a failed fundoplication requires revisional surgery. The most common indications for reoperation are a herniated fundoplication into the mediastinum or a "slipped" fundoplication. A slipped fundoplication occurs when the fundoplication can slip down onto the stomach resulting in recurrent reflux and possible obstruction. The diagnosis is often made by an esophagram or endoscopy. Figure 7.6 shows the hourglass appearance of a slipped fundoplication on barium esophagram. Although they can be effective, reoperations are associated with a higher complication rates, longer operative times, and higher conversion rates from laparoscopic to open [53, 54]. Despite these risks, patient satisfaction following revisional surgery is approximately 89% and resolution of typical reflux symptoms is achieved in 85% of patients [55]. Therefore, if revisional surgery is needed, there is a strong likelihood that success can be achieved in these patients.

7.7.3 Shortened Esophagus

Lack of axial tension is critical for minimizing the failure of a fundoplication. This is primarily achieved by obtaining adequate intra-abdominal esophageal length during dissection. When the intra-abdominal length of the esophagus is less than 2–3 cm, often referred to as a short esophagus (SE), successful fundoplication is difficult without additional maneuvers. Sometimes, an SE can be discovered during the preoperative evaluation on endoscopy, contrast radiography, or manometry. The first step in treating the SE is additional mediastinal dissection. The extent of

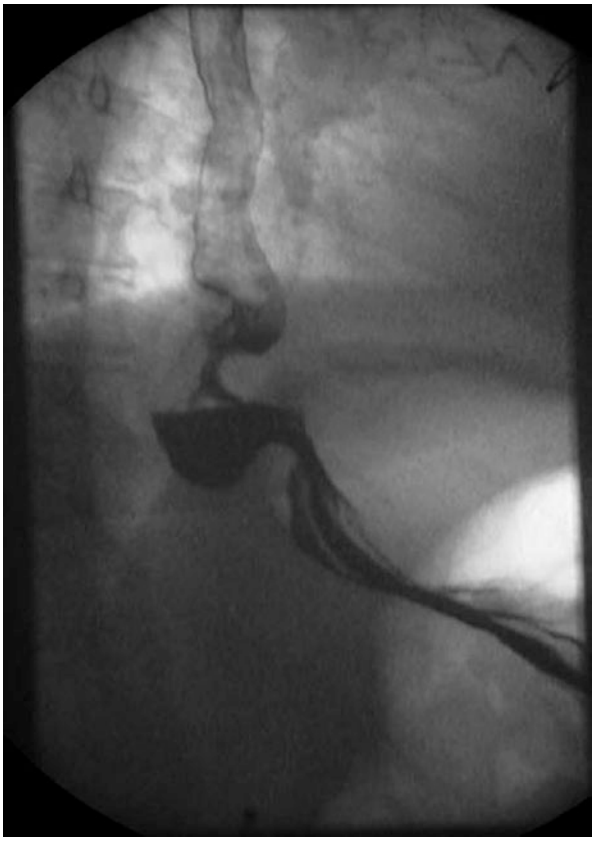

Fig. 7.6 Hourglass appearance of slipped fundoplication on esophagram

mediastinal dissection needed to obtain necessary esophageal length can vary. A useful system classifying the extent of dissection needed for this mobilization has been described. A type I dissection extends less than 5 cm beyond the hiatus, type II extends beyond 5 cm, and type III is when the GEJ cannot be mobilized greater than 2 cm below the hiatus. All type III dissections require an esophageal lengthening procedure [56].

Several variations of the Collis gastroplasty have been described [56, 57]. Whether they are performed purely intra-abdominally or through a combined laparoscopic–thoracoscopic approach, the general principle remains the same. Lengthening of the esophagus involves stapling the fundus next to the esophagus to create a neo-esophagus with adequate intra-abdominal length (Fig. 7.7). This additional maneuver ensures that appropriate intra-abdominal esophageal length can be attained so that a successful fundoplication may be completed. Excellent long-term symptom resolution with respect to heartburn, regurgitation, dysphagia, and chest pain have been reported following this intervention, however one needs to be aware that this nonphysiologic solution results in high rates of postoperative esophagitis due to the iatrogenic ectopic gastric mucosa [58, 59].

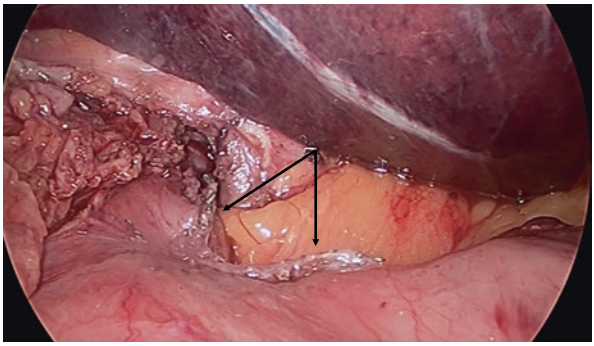

Fig. 7.7 Collis gastroplasty. → (arrows) = staple line along esophagus and fundus of the stomach

7.8 Conclusion

GERD not only causes a number of unpleasant symptoms such as heartburn and regurgitation but carries a real cancer risk if left untreated. Surgical interventions are often necessary in patients who fail medical therapy, have complications secondary to GERD, or suffer from persistent extra-esophageal manifestations of the disease. Surgery is an option as well for the increasing number of patients who wish to be off daily PPIs. Laparoscopic fundoplication is the gold standard for the surgical treatment of severe GERD and has a satisfaction rate in >90% of patients who undergo a fundoplication. Although the Nissen fundoplication has the best acid-reducing potential, we recommend a tailored approach when deciding which fundoplication should be performed that should be based on the degree of symptoms, dysfunctions in esophageal motility, and risk for developing postoperative complications. In all of these operations, it is vital to restore competence to a malfunctioning LES as well as repair any potential hiatal hernia that may be present. The surgeon must also take into consideration special situations that may arise when dealing with obesity, revisional operations, or patients with a short esophagus.

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Anti-Reflux Surgery II: Magnetic Sphincter Augmentation—LINX®

8

Ivan Kristo and Sebastian F. Schoppmann

8.1 Introduction

Gastroesophageal reflux disease is a condition that develops when reflux of gastric contents causes troublesome symptoms and/or complications [1]. From a pathophysiological point of view, adverse lifestyle and rising obesity within the Western world induce gastric overdistension consecutively leading to damage and shortening of the lower esophageal sphincter (LES). It is widely accepted that increasing structural deficiency of the LES not only leads to GERD but also has an impact on the severity of disease [2]. Therefore, surgical efforts are focused to restore a sufficient barrier function.

First concepts using a foreign body around the LES were integrated in the Angelchik prosthesis, which was initially promising for patients with GERD [3]. Nevertheless, swallowing against a solid body led to severe complications including esophageal perforation requiring major surgical resections.

Within the last years, several patient-adapted surgical tools were put on the market with the attempt to overcome these limitations. The magnetic sphincter augmentation (LINX®; Johnson & Johnson, New Brunswick, New Jersey, USA) represents one of these novel instruments: It consists of magnetic beads that are linked to each other in a ring-like shape and sized according to the patients' esophagus. In contrast to the Angelchik prosthesis, while swallowing beads are diverging, magnetic force is decreasing which limits energy that potentially negatively impacts the esophagus.

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_8

Furthermore, a device may also provide a more uniform implantation as it is less affected by surgeon or center, a fact that is important in patients undergoing laparoscopic anti-reflux procedures [4]. This chapter is supposed to give you a short overview about current knowledge and ongoing research concerning magnetic sphincter augmentation (MSA).

8.2 Surgical Implantation

The implantation of the LINX® device is conducted via a minimal-invasive laparoscopic approach [5]. After dissection of the *pars flaccida* of the *omentum minus,* the right crus of the diaphragm is exposed. Hereupon, the phrenico-esophageal ligament is dissected to gain control of the left crus and make identification of the anterior and posterior vagal nerve possible. A window between the esophageal wall and the posterior vagal nerve is created and used to place a seizing device that suggests the appropriate diameter and size of the LINX® device (see Fig. 8.1). The chosen device is hereupon inserted around the gastroesophageal junction and closed via a 3D securing mechanism (see Fig. 8.2).

8.3 Current Evidence

Initial target groups were clearly patients with rather limited GERD. Studies included patients with abnormal esophageal acid exposure and typical symptoms of GERD that responded at least partially to proton pump inhibitors. Hiatal hernias were limited to less than 3 cm, whereas high-resolution manometry had to document regular esophageal motility. Presence of Barrett's esophagus, previous anti-reflux surgeries, and advanced esophagitis noted during endoscopy were clear exclusion criteria.

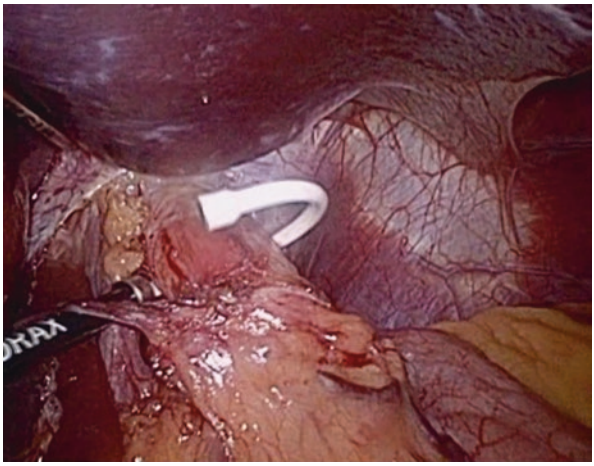

Fig. 8.1 Measurement for correct size (above)

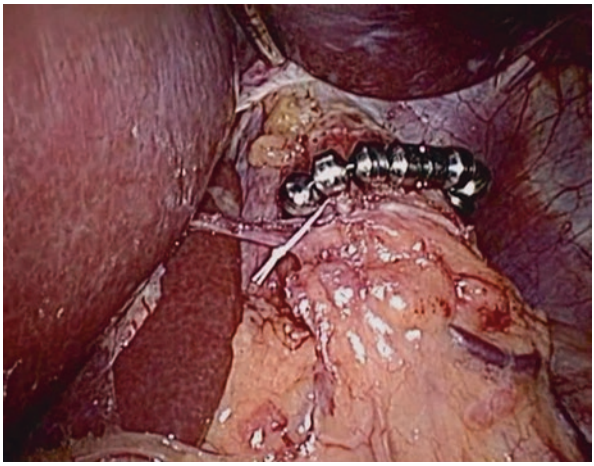

Fig. 8.2 Correctly implanted LINX (below)

Safety and efficacy were demonstrated in 2008 in a trial published by Bonavina et al., where 38 patients underwent magnetic sphincter augmentation [6]. Surgical procedures were uneventful with all patients being discharged within 48 h. After a mean follow-up of 209 days, outcomes were promising. GERD Health-Related Quality of Life (GERD-HRQL) scores decreased from 26 to 1 with 89% of patients being off anti-reflux medications. This increase in quality of life was based on normalization of esophageal acid exposure in 79% of participants, whereas ability to belch was preserved in all of them, a fact that is not given after fundoplication. Nevertheless, mild dysphagia was reported in 45% of patients at a short-term follow-up. After 1 and 2 years, the feasibility trial was reevaluated with 90% and 86% of patients being off PPI, respectively [7]. Normalization of acid exposure was acquired in 90% after 2 years, which was also reflected in patient satisfaction rates close to 90%. Only one device had to be removed due to persistent dysphagia. Device removal was possible without anatomic changes, pointing out that different treatment escape options are still possible after failed magnetic sphincter augmentation. Additionally, no migration, erosion, or mucosal damage was noted. Intermittent mild dysphagia, limited to the first 3 months was again described with sufficient acid control after 4 years of follow-up [8]. These striking results led to a pivotal study that prospectively assessed 100 patients with limited GERD before and after LINX® implantation [9]. Investigators aimed for a normalization or reduction of acid exposure of at least 50% at 1 year. This outcome parameter was achieved in 64% of study participants with improvement of quality of life in 92% of patients. Again, dysphagia, observed in 68%, was the main contributing factor for device removal in three patients with another three patients undergoing revisional surgery due to incomplete symptom control and vomiting.

As a consequence, a new therapeutic option for patients with inadequate medical symptom control and limited GERD was available.

Currently, researchers are trying to extend limitations of this novel device. For example, the Lipham group described the implementation of magnetic sphincter

augmentation in patients with large hiatal hernias and concomitant hiatal repair. Interestingly, they found that patients with large hiatal hernias even benefitted better from LINX® implantation when compared with patients with small hernias [10]. Even in advanced and complicated GERD, magnetic sphincter augmentation seems to be a powerful tool [11]. Alicuben et al., retrospectively analyzed a patient cohort with biopsy-proven intestinal metaplasia. After a median follow-up of 1.2 year, 71.6% of patients experienced regression of intestinal metaplasia. There was no progression to dysplasia or carcinoma. Patients with abnormal DeMeester scores and long-segment intestinal metaplasia were prone to persist. Nevertheless, long-term follow-up in these patients is impatiently awaited.

Recently, randomized controlled trials investigated LINX® versus medical treatment for patients with regurgitation. Bell et al., included 150 patients in a prospective trial at 21 US sites and randomized patients in a 2:1 fashion either to twice-daily PPI therapy or to laparoscopic MSA [12]. At 6 months, relief of regurgitation was superior in the MSA group (82% versus 10%), which led to the conclusion that patients that suffer from moderate-to-severe regurgitation, despite PPI therapy, should be considered for MSA rather than dose escalation. Consistently, after 1 year, outcomes did not change [13].

These data allow to extend the use of MSA as even long-term safety informed indicated a low removal rate of 0.15% due to erosion with no device migration being reported after over 3000 implantations [14].

8.4 Magnetic Sphincter Augmentation or Fundoplication?

When a novel disease is implemented for the treatment of GERD and offers excellent outcomes, comparative studies to the current gold standard, namely laparoscopic fundoplication, are of high interest. Riegler et al., reported prospective multicenter outcomes of MSA and fundoplication for the treatment of GERD [15]. After 1 year, quality of life was similar in both groups, whereas MSA was superior in controlling regurgitation and cessation rates of PPI. Interestingly after MSA, gas bloating rates were lower and the preserved ability to vomit, if needed, were higher. Therefore, reduction of postoperative gas bloating, a fact that limited the use of fundoplication so far, seems to be a big advantage of MSA. However, it has to be noted that groups were not homogeneous as the fundoplication group included patients with advanced GERD. A matched analysis tried to overcome this limitation and retrospectively included patients in a case-controlled study of MSA and Nissen fundoplication [16]. MSA was associated with shorter operative times, which seems more than reasonable as the implantation process is minimal-invasive and does not change anatomy. The authors noted that both groups resulted in good symptom control and improvement of quality of life. Nevertheless, MSA preserved a more physiological lower esophageal sphincter and was superior as far as preserved belching is concerned and may therefore explain reduced gas bloating rates after MSA. Similar results were observed in other comparative trials, where gastrointestinal side effects were lower after MSA [17–19]. Importantly, dysphagia rates were

reported to be higher after MSA when compared to fundoplication. However, dysphagia presented mainly mild and self-limiting within the first 3 months, suggesting an adaptation process to a foreign body.

8.5 Conclusions

Concluding, MSA represents a promising novel tool in patients with GERD and surely enriches the surgical therapeutic pool. It offers symptom control with high rates of normalization of esophageal acid exposure and cessation of PPIs. An excellent safety profile combined with long-term efficacy result in improved quality of life. Currently, limits of this new technique are explored and its field of application is extended. When compared to laparoscopic fundoplication, MSA offers lower rates of gastrointestinal side effects as gas bloating, due to a more physiological approach and unchanged anatomy. Additionally, a more uniform implantation process with a steep learning curve could offer better comparable outcomes between centers and surgeons. Nevertheless, dysphagia, although mostly mild and self-limiting, occurs rather frequently after MSA. The appropriate ring size and preexisting dysphagia as potential risk factors for postoperative dysphagia may be able to reduce these numbers.

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Anti-Reflux Surgery III: Endoscopic Fundoplications

9

Erwin Rieder

9.1 Introduction

Gastroesophageal reflux disease (GERD) is a common disorder and is associated with a significant decrease in quality of life (QOL) [1]. It is known to affect up to 20% of the Western population [2]. Either symptomatic therapy with proton pump inhibitors (PPI) or more causative treatment by conventional anti-reflux surgery has been shown to be effective. Although data remain contradictory, PPI may be cancer protective [3] but might also lead to eventual long-term adverse events [4]. Additionally, PPI are not addressing the underlying anatomical defect and simultaneously leads to inadequate control of symptoms such as regurgitation. The surgical mainstay to treat GERD has been laparoscopic fundoplication, which, however, is invasive and might lead to adverse events, such as dysphagia, gas bloat syndrome, or recurrent reflux in the long term [5]. Today, only a small proportion of GERD patients are finally treated by conventional anti-reflux surgery. This leads to a group of patients, who are either not willing to be treated by or are not effectively treated with PPI but simultaneously do not want to run the potential risks of conventional surgery [6]. In the last two decades, endoscopic therapies have emerged to bridge this treatment gap between laparoscopic fundoplication and chronic medical management of GERD. Some of which have not withstood clinical tests due to several reasons [7], but with some still or again available and in clinical use. Today, both pharmacological and surgical shortcomings have led medical as well as surgical societies to acknowledge the role of endoscopic GERD therapies for selected patients [8, 9], which have evolved with enormous innovations in endoscopic tools and treatment options. All of them invented to challenge standard anti-reflux

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_9

surgery but foremost might provide a less destructive option to treat GERD simultaneously providing the opportunity of a personalized surgical anti-reflux therapy [10, 11].

9.2 Techniques and Results

The general technical concept of all plication devices to treat GERD is the endolumenal creation of a serosa-to-serosa plication using either tags or staples to reinforce an insufficient "anti-reflux valve."

One of the first commercially available devices for endoscopic plications was the NDO Surgical plicator (NDO Surgical Inc., Mansfield, MA). It was built to deliver a transmural suture for serosal apposition and full thickness plication at the cardia. Patient factors predictive of 24-h pH normalization have been analyzed [12]. Khajanchee and colleagues identified a body mass index below 30, an initial DeMeester score under 30, and a heartburn score smaller than two to be predictive for successful endoscopic fundoplication. This group of patients had a normalized DeMeester score in more than 80% of patients compared to no normalization if patients had higher BMI, higher pre-plication DeMeester score, or more severe heartburn. However, this device is no longer available commercially.

Based on a similar plicator technology, a modified endoscopic full thickness plication device was reintroduced more recently by a different manufacturer (GERD-X, G-SURG GmbH, Seeon-Seebruck, Germany). In early small study evaluation, it was found to improve subjective as well as objective parameters at the 1-year follow-up. Refinements of the device as well as technique are still under investigation. The device uses hydraulic technique for control and is used with a small diameter endoscope, which is introduced into the stomach. Along with the device it can be retroflexed to manipulate and retract the gastric cardia into the two arms of the plication tool and deploying sutures after gathering sufficient tissue (Fig. 9.1a, b). Multiple sutures are used to create an augmented anti-reflux valve [13, 14]. The authors described significant improvement in symptoms, QOL, and DeMeester scores, with six patients requiring anti-reflux surgery within 3 months due to persistent symptoms. Few serious adverse events such as hematoma, pneumonia, intractable pain, and a Mallory-Weiss tear were reported [15]. Although the plicator appears promising to reduce symptoms in the short-term, long-term results and randomized trials are necessary to evaluate its role in the management of GERD.

The majority of data, so far, have been available on the transoral incisionless fundoplication (TIF) procedure using the EsophyX device (EndoGastric Solutions, Redmond, WA, USA). It was originally described in 2005 and has had several modifications until 2009 (TIF 2.0).

This device also uses a helical retractor and an additional integrated suction apparatus to grasp the distal esophagus, delivering up to 12–23 H-shape polypropylene fasteners to create a 2–3 cm, 270° full thickness esophagogastric fundoplication above the Z-line in the current version (Fig. 9.2a, b). Objective data have shown that the TIF 2.0 device led to better results compared to older versions [16]. A recently

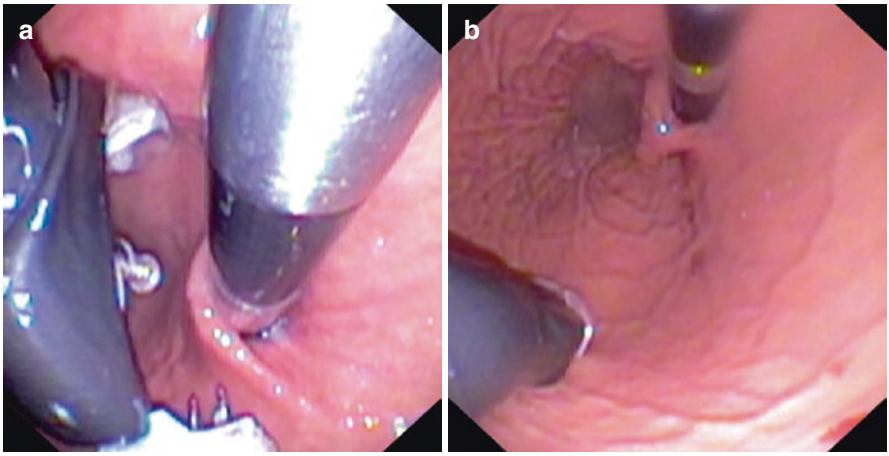

Fig. 9.1 (**a**) The GERD-X device is retroflexed to manipulate and retract the gastric cardia into the two arms of the plication tool. (**b**) Using a small diameter endoscope within the GERD-X device for visualization, the retroflexed view demonstrates the "esophagogastric valve" after the sutures have gathered sufficient tissue

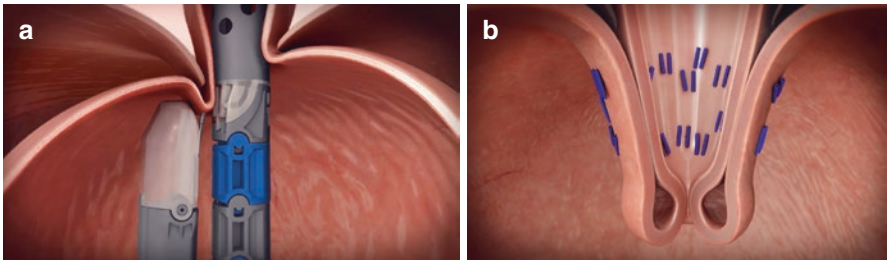

Fig. 9.2 (**a**) The distal esophagus is retracted into the Esophyx® device to deliver the fasteners (schematic drawing). (**b**) Multiple H-shaped fasteners were delivered to create a 270° full thickness esophagogastric fundoplication (schematic drawing)

published systematic review, comparing the TIF procedure with a PPI/sham control group, found a significantly higher response rate to TIF [17]. However, no significant difference in the mean percentage of esophageal acid exposure time was observed. In this meta-analysis, response rate efficacy was found to decrease over time. In contrast, data published more recently could demonstrate more encouraging results with regard to the long-term outcomes of TIF. Two long-term follow-up studies found clinical remission in the majority of patients at a median follow-up of 59 and 97 months. On the other hand, PPI consume did also re-increase over time [18, 19]. Also, the TEMPO trial could confirm the durability of the TIF 2.0 procedure. In their long-term analysis, the resolution of troublesome regurgitation was achieved in 86% after 5 years [20]. The resolution of atypical symptoms was still eliminated 80% after 5 years, with only 34% of patients on daily PPI compared to

100% at initial screening. The incidence of serious adverse events, such as perforations or bleedings appeared to be as low as 2.4% [17]. Although GERD symptoms seem to improve, it appears that objective improvement of distal esophageal acid exposure cannot be achieved and was only normalized in 29% at 12 months, as described by others [21]. Overall, current evidence demonstrates that the TIF procedure is capable to eliminate GERD symptoms in the majority of selected patients with a low incidence of serious adverse events, but objective improvement in distal esophageal acid exposure could not be clearly demonstrated. However, when TIF is used as initial therapy, potentially necessary conventional fundoplication appears not to be impaired [22].

A completely different technology is used by the MUSE (Medigus, Omer, Israel) endoscopic stapling device, which consists of built-in video camera, an endostapler, and an ultrasound transducer. The ultrasound-based range finder helps in assessing the tissue thickness before firing the staples (Fig. 9.3a, b). The stapler is then fired at the level above the esophageal Z-line and repeated several times to form a sufficient fundoplication. So far, available evidence is mainly limited with regard to the safety and efficacy of the device. Zacherl and colleagues reported the 6-month results of 66 patients in a prospective multicenter trial and found improvement in the GERD Health-Related Quality of Life score as well 65% of patients off PPI. However, there were eight severe adverse events recorded within the first 24 patients, with two who required re-intervention [23]. This led to technical and protocol changes, with no further cases of leak or pneumo-mediastinum in the next 48 subjects enrolled. Kim et al., found nearly 70% of patients remaining off PPI after 4 years. No residual severe adverse events were observed after the 6-month follow-up [24] but no long-term pH studies were reported.

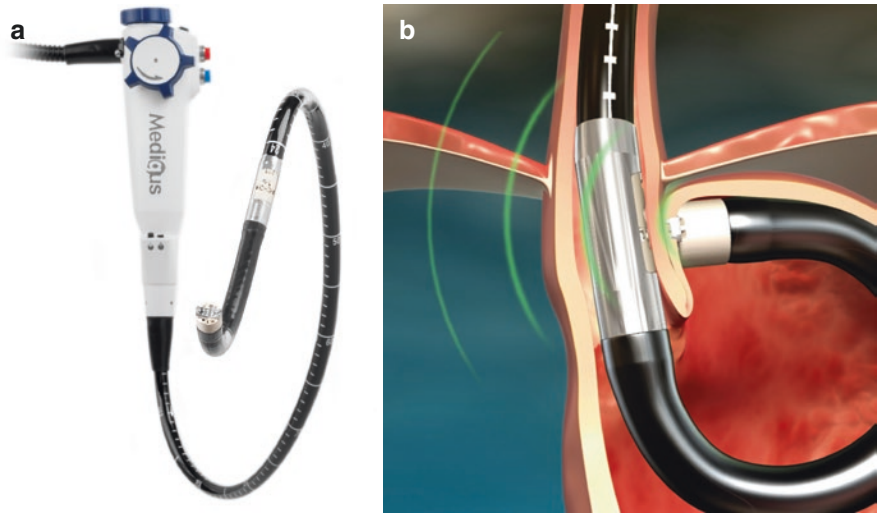

Fig. 9.3 (**a**) The flexible MUSE system uses an endoscopic stapling device, which consists of built-in video camera, an endostapler, and an ultrasound transducer. (**b**) The distal esophagus is retracted into the ultrasonic-guided stapler device (schematic drawing)

9.3 Conclusion

Overall, endoscopic fundoplication could be an alternative therapy for highly selected patients. Hereby, proper patient selection is mandatory to achieve appropriate results from endoscopic fundoplications. As potentially later conventional fundoplication seems not to be impaired with some procedures, it could also nicely serve as initial nonmedical therapy in some patients. Current data on improvement of objective parameters such as esophageal acid exposure are still missing. As long-term reflux symptom control efficacy also appears to decrease with time, the appealing option of an endoscopic fundoplication has certainly to be a matter of continued research.

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Redo Fundoplication

10

Luigi Bonavina, Emanuele Asti, and Daniele Bernardi

The definition of surgical success and failure of fundoplication for gastroesophageal reflux disease with or without hiatus hernia vary considerably in the literature. Inappropriate patient selection and choice of the operative procedure, as well as technical errors occurring during the course of the operation, may account for failure of the primary repair. Eventually, 3–6% of patients complaining of severe symptoms and/or mechanical wrap complications require revisional surgery [1–3].

Laparoscopic Nissen fundoplication has been for several decades the gold standard surgical procedure for GERD. It is a safe, effective, and durable anti-reflux procedure when performed in specialized centers. A multicenter European trial comparing medical therapy with fundoplication performed by expert surgeons has shown that 92% of medical patients and 85% of surgical patients remained in remission at 5 years of follow-up [4]. Despite a remarkably low morbidity and mortality rates, the operation is still underused due to the perception of long-term side effects and fear of failure [5]. Also, wide variability in clinical outcomes related to interindividual surgical expertise and/or non-standardized technical modifications have restricted the adoption of laparoscopic fundoplication mainly to patients with severe long-lasting disease and large hiatal hernia [6]. A negative trend in the utilization of laparoscopic surgical fundoplication has been reported in the United States over the past decade [7, 8], and many surgeons have moved away from the Nissen in favor of the Toupet partial fundoplication. More recently, the laparoscopic LINX procedure has emerged as a possible alternative to fundoplication in selected patients [9, 10].

Results of remedial operations for persistent or recurrent symptoms following anti-reflux surgery are generally less satisfactory compared to the primary

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_10

procedure, especially after multiple failed surgical attempts [11–13]. This is related to the difficulties in recognizing the pattern of failure and to the inherent technical difficulties due to adhesions and gross anatomical distortion from the previous operation. When the cause of failure has been properly identified and addressed by an appropriate surgical technique, the majority of patients can benefit from a reoperation [14, 15].

10.1 Prevention of Fundoplication Failures

There are four categories of errors that can cause immediate, early, or late failure of the anti-reflux repair. Awareness of such potential mistakes can reduce the complication rate and the need for reoperation.

Wrong patient selection. Most surgical failures can be prevented if patients are properly selected and procedures are properly performed. It is important to make sure that preoperative symptoms are clearly related to gastroesophageal reflux and not to achalasia, gallstones, irritable esophagus, myocardial ischemia, etc. The accuracy of endoscopy is quite limited in this setting and, therefore, especially in the absence of typical symptoms, the preoperative work-up should always include esophageal manometry and ambulatory esophageal pH monitoring.

Wrong choice of operative procedure. The pattern of esophageal motility should be carefully investigated and a potentially obstructive Nissen fundoplication be avoided when the patient complains of dysphagia and/or there is evidence of an esophageal body motility disorder or a high outflow resistance at the gastroesophageal junction. In such circumstances, a Toupet fundoplication is expected to cause less obstruction and is better tolerated, especially by female patients [16].

Wrong surgical technique. Failure to adequately mobilize the distal esophagus and fundus to recognize a true shortened esophagus, to properly repair the hiatus, and to properly construct the fundoplication may be the reason for recurrence. Esophageal shortening may result in misidentification of the gastroesophageal junction and placement of the fundoplication around the proximal stomach rather than at the gastroesophageal junction. Although this is often called a "slipped Nissen," it should be considered a misplaced rather than a slipped wrap. Recognition of the fat pad around the angle of His and liberal use of intraoperative endoscopy can help to identify the true gastroesophageal junction. Intraoperative confirmation of a true short esophagus should alert the surgeon to perform a Collis lengthening procedure instead of a standard fundoplication. Disruption of the fundoplication is another common reason of technical failure of the primary repair and may be due to excessive radial tension especially when the short gastric vessels have not been divided and only the anterior fundic wall has been used. In fact, the laparoscopic Nissen-Rossetti fundoplication has been associated to a higher failure rate, especially during the learning curve phase [17]. Herniation of the wrap in the mediastinum with an intact fundoplication occurs as a result of excessive longitudinal tension or inadequate closure of the hiatus. Other causes of failed anti-reflux surgery include a too long and/or tight fundoplication and a twisted fundoplication that can cause severe postoperative dysphagia, which is usually refractory to dilatation.

Wrong postoperative management. Immediate surgical failures are commonly the result of uncontrolled postoperative nausea and vomiting causing abrupt rises in intra-abdominal pressure and subsequent mediastinal migration of the wrap. Early failures can occur also as a result of sentinel events such as heavy lifting, abdominal straining, or trauma. Control of early retching and vomiting is critical after anti-reflux surgery. It has been found that about one-third of patients with early retching developed mediastinal herniation of the wrap requiring revisional surgery [18]. Avoiding the use of nasogastric tubes and opioids, and routine application of a pharmacologic protocol including dexamethasone and metoclopramide, can reduce the incidence of this complication.

10.2 Assessment of Failed Anti-Reflux Surgery

Exhaustive evaluation of recurrent or persistent symptoms and correlation of symptoms with the presurgical status and current anatomic and pathophysiological abnormalities are the crucial steps before considering a reoperation. The most common postoperative complaints are dysphagia, heartburn, and abdominal discomfort related to meals. It is important to remind that all these symptoms may be present during a normal postoperative course, especially in the first 3 months after surgery. Most symptomatic failures, such as the slipped Nissen with "hourglass" stomach, are usually observed in the first 2 years after the initial procedure and half of them will undergo reoperation within 5 years [19]. Late mediastinal migration of the wrap is frequently observed in patients operated for large type III hiatal hernia, but it may not require correction if the hernia is small and asymptomatic [20, 21].

Anatomical assessment is based on endoscopy, barium swallow study, and CT scan to evaluate the presence of strictures, paraesophageal hernia, and the anatomical status of the previous fundoplication [22]. Functional assessment includes esophageal manometry and ambulatory esophageal pH-impedance monitoring to evaluate the presence of a motility disorder or persistent gastroesophageal reflux, respectively. High-resolution manometry allows to identify abnormalities not seen on conventional perfused manometry, such as the double-hump configuration of the high-pressure zone that indicates spatial separation and implies sphincter failure [23, 24].

Indications to reoperation should be based on the patient's physiological state, the severity of symptoms, and the response to conservative therapy. In most patients with refractory reflux or dysphagia combined with mechanical outflow resistance, a reoperation is mandatory due to the risk of respiratory complications and even pulmonary fibrosis secondary to aspiration [25].

10.3 Remedial Surgery

The revisional procedure should be tailored to the individual patient by considering a number of factors: reasons for failure of the first operation, esophageal length, peristaltic reserve, presence of Barrett's esophagus, and concomitant gastric

pathology. In most patients, laparoscopic fundoplication revision is feasible, although the procedure is generally expected to be long and tedious due to the adhesions of a previous laparotomy and the difficulties that may be encountered in the takedown of the fundoplication. Esophageal resection should only be considered in patients with multiple previous repairs, extensive fibrosis with stricture refractory to multiple endoscopic dilatations, and evidence of dysplasia on Barrett's esophagus [26].

In patients with a slipped/misplaced Nissen and/or chest herniation of the wrap attention should be directed first to assess the tissue quality of the crura and to consider the opportunity of mesh reinforcement [20, 21] and/or crural relaxing incisions [27]. Some individuals may require an esophageal lengthening procedure combined with re-fundoplication if the esophagus is found to be truly short. Complete takedown of the old repair is a mandatory step. A stapled wedge resection of the gastric fundus provides a safe esophageal elongation and is easier to perform and to teach compared to the Steichen "buttonhole" technique, requiring both circular and linear stapling, and to the trans-thoracic gastroplasty [28, 29]. In patients with excessive longitudinal tension, truncal vagotomy has been proposed as a safe alternative to the Collis gastroplasty [30].

In patients with impaired esophageal motility (>30% synchronous esophageal waves or mean amplitude less than 30 mmHg, or criteria of ineffective esophageal motility at high-resolution manometry), a partial 270° Toupet rather than a 360° Nissen fundoplication may be an option. An esophageal myotomy combined with a Dor fundoplication is usually performed in patients with previously misdiagnosed achalasia [31, 32].

In some patients, a re-fundoplication cannot be performed because the fundus is inadequate. An alternative surgical strategy, especially after multiple previously failed surgical attempts, consists of vagotomy, antrectomy, and Roux-en-Y reconstruction to effectively reduce both acid and alkaline components of the refluxate [33]. Laparoscopic gastric bypass is an alternative option that can be considered in obese patients [34]. Pyloroplasty, or even a total gastrectomy in extreme cases, may be indicated in patients who present with severe gastroparesis possibly related to inadvertent vagotomy at the time of the index operation [35].

10.4 Techniques of Laparoscopic Revisional Surgery

Historically, reoperations for failed anti-reflux procedures were performed through an open trans-abdominal or trans-thoracic technique. Today, more redo operations are performed laparoscopically. All redo procedures should be considered complex and should be scheduled as the first case of the day. On-table endoscopy is routinely performed after induction of anesthesia, and the scope is left in the esophagus for intraoperative evaluation. Adhesiolysis between the stomach and the liver and around the hiatus should be very careful to avoid visceral perforations and injury to the vagal trunks. Full mobilization of the fundoplication is

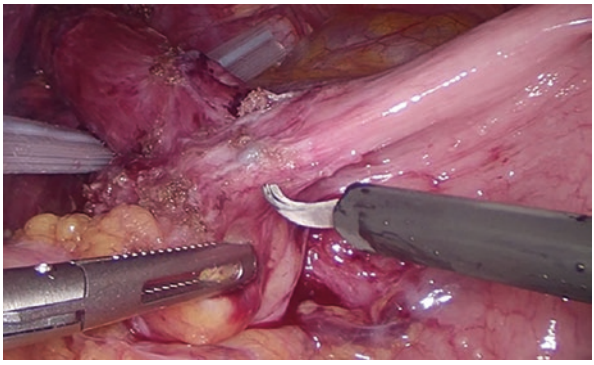

Fig. 10.1 Take down of a misplaced Nissen fundoplication with complete separation of the two valves from the gastric body

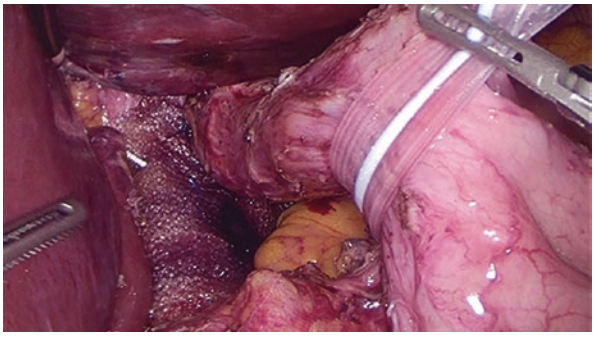

Fig. 10.2 After completing the posterior hiatoplasty with interrupted nonabsorbable stitches, a synthetic absorbable mesh (PHASYX®) is placed over the crura repair

performed by removing the crural sutures and by taking down residual short gastric vessels. A linear stapler can help dividing the two halves of the wrap. The fat pad should be routinely excised to identify the true gastroesophageal junction and a 3-cm tension-free intra-abdominal esophageal segment should be obtained. (Fig. 10.1). Care should be taken to minimize tension on the crura repair by clearing the entire surface of the right crus and decrease the insufflation pressure to less than 10 mmHg to facilitate approximation of the crura. The hiatus is repaired with interrupted nonabsorbable stitches and placement of a composite or synthetic absorbable mesh should be considered (Fig. 10.2). A total or partial fundoplication is then performed (Fig. 10.3).

If a short esophagus is suspected, a modified Collis wedge gastroplasty procedure can be performed. Once the gastric fundus has been completely freed from posterior and lateral adhesions, a bougie is inserted in the esophagus under direct laparoscopic visualization and placed across the gastroesophageal junction along the lesser curve. The fundus is retracted inferiorly to the patient's left side, and sequential fires of a linear stapler are directed toward the bougie to a point 3 cm below the gastroesophageal junction. The gastroplasty is then completed by resecting the wedge of fundus with the stapler applied parallel to the bougie toward the angle of His. A fundoplication around the neo-esophagus concludes the procedure (Fig. 10.4).

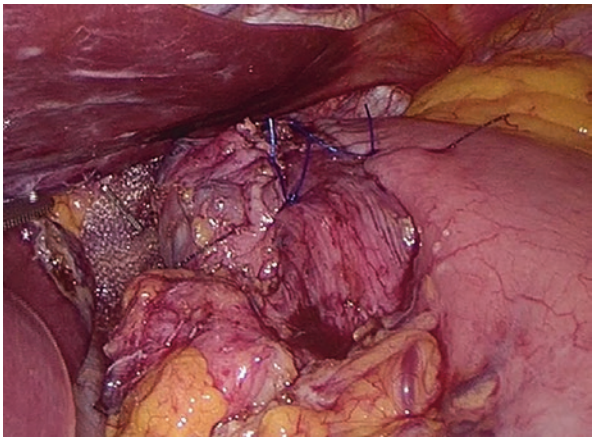

Fig. 10.3 Completed Toupet fundoplication

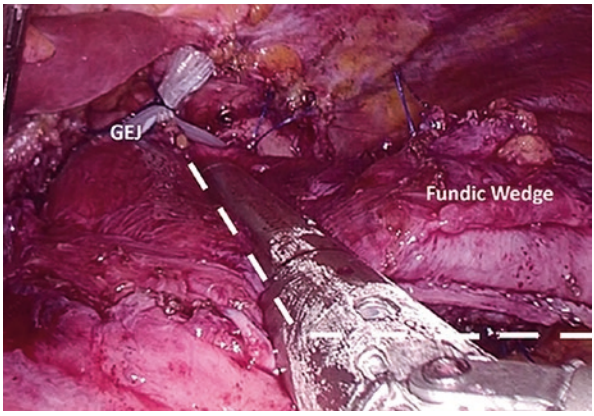

Fig. 10.4 Wedge Collis gastroplasty. A linear stapler is applied across the upper fundus toward the lesser curve; the gastroplasty is completed by applying the stapler parallel to the lesser curve toward the angle of His

10.5 Outcome of Laparoscopic Revisional Surgery

A systematic review and meta-analysis of laparoscopic revisional anti-reflux surgery, including 19 case series and one case-control study, reported on 922 patients operated operated between 1990 and 2010 [36]. The mean surgical duration was 166 min and the conversion rate to open revision 7%. The most common indication to reoperation was reflux (61%) followed by dysphagia (31%), gas bloat syndrome (4%), regurgitation or vomit (3%), and chest pain (2%). The most common anatomic problem found at reoperation was mediastinal migration of the wrap. Nissen fundoplication was performed in 70% of patients. The overall complication rate was 14% (0–44%). A satisfactory to excellent result was reported in 84% of patients, while 5% of patients required further surgery.

10.6 Fundoplication After Removal of Linx Device

An analysis of the safety profile of the first 1000 worldwide implants of the magnetic sphincter augmentation device (LINX procedure) in 82 hospitals showed 1.3% hospital readmission rate, 5.6% need of postoperative endoscopic dilations, and 3.4% reoperation rate [37]. A more recent study reported the technique and the long-term results of one-stage laparoscopic removal and fundoplication [38]. Once the scar tissue at the gastroesophageal junction corresponding to the site of the LINX implant is identified, a monopolar electrocautery hook is used to cut the scar tissue and to expose a pair of anterior titanium beads. The independent titanium wire connecting the beads is cut with ultrasonic scissors, and one bead is grasped with an Endo Clinch and retracted upward. This allows step-by-step cutting of the thin fibrous capsule overlying each bead and pulling out of the device. The total bead count in the explanted device is confirmed and the device removed through a 10 mm port. Intraoperative endoscopic assistance helps to check the integrity of the esophageal mucosa during and after removal, and/or to assist during retrieval of the beads migrated into the esophageal lumen. A concurrent anti-reflux repair (partial or total fundoplication) can then be performed. Out of 164 patients implanted with a LINX device, 11 (6.7%) were explanted at a later date. The main presenting symptom requiring device removal was recurrence of heartburn or regurgitation in 46%, dysphagia in 37%, and chest pain in 18%. In two patients (1.2%) full thickness erosion of the esophageal wall with partial endoluminal penetration of the device occurred. Device removal was most commonly combined with partial fundoplication. There were no conversions to laparotomy; the postoperative course was uneventful in all patients and the GERD-HRQL score returned to normal limits at 12–58 months after surgery.

10.7 Conclusions

Revisional surgery after fundoplication is complex, requires good surgeon's judgment and expertise, but is generally feasible laparoscopically. Accurate preoperative and intraoperative assessment is necessary to identify the cause of the failure and to tailor the procedure to the individual patient. With the rising epidemic of gastroesophageal reflux disease, reoperative hiatus surgery remains a challenge whose complexity and volume is expected to remain stable or to increase in the future.

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Diagnosis of Barrett's Carcinoma: Role of Diagnostic Imaging

11

Dietmar Tamandl

11.1 Introduction

Imaging plays an important role in the management of distal esophageal cancer (EC) and adenocarcinoma of the gastro-esophageal junction (GEJ), arising from Barrett's esophagus, which will be termed Barrett's carcinoma (BC) for the purpose of this chapter. The main role of radiology is to distinguish between early and locally advanced cancers and to rule out or confirm distant metastatic disease [1]. The method with the highest diagnostic accuracy should be chosen to assess patients at any stage of BC [2]. Before any surgical or endoscopic intervention, the locoregional situation has to be assessed and an optimal treatment plan can be generated. After neoadjuvant therapy either comprising of chemoradiotherapy (CRT) or chemotherapy, restaging using computed tomography (CT) or positron emission tomography (PET)-CT can help to identify responding and nonresponding tumors, with possible implications on management [3]. If possible, a clinical tumor stage (TNM) should be assessed after obtaining the best staging information present. Currently, as of 2020, the eighth edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC), TNM staging system should be used for this purpose [4, 5]. After surgery, radiological methods must be available to assess for complications and to aid in the therapeutic management [6].

The role of various radiological methods both in pre- and post-therapeutic staging is demonstrated in this chapter and possible diagnostic pathways in BC are discussed.

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_11

11.2 Diagnosing Barrett's Carcinoma

The diagnosis of BC is exclusively done by endoscopy and biopsy of the suspicious region. In early BC, cross-sectional techniques have no role in establishing the locoregional tumor stage or delineating the extent of neoplastic disease. In the area of the distal esophagus or GEJ [7], endoscopic ultrasound (EUS), in combination with endoscopy and biopsy, is the method of choice for locoregional staging of early BC and will be discussed in the respective chapter. Diagnostic imaging comes into play when tumors become visible e.g. on CT, which is usually the case from stage-T2 onwards [8]. Nevertheless, even in stage T1b EC, lymph node metastases already occur in 23% [9], which in turn raises the possibility of distant metastases and would therefore necessitate a proper staging examination of the chest and abdomen. A CT scan should include the neck, chest, and abdomen in order to cover all respective areas of involvement [2] and to rule out second upper gastrointestinal neoplasms [10]. The strengths of imaging methods like CT or PET/CT are assessment of locoregional tumor extension beyond the esophagus or GEJ and the detection of metastatic disease [11]. Except for very early or in situ carcinoma, these modalities are employed in every patient for the diagnosis, treatment assessment, and follow-up of Barrett's carcinoma [12, 13].

11.3 Fluoroscopy

In the last century, fluoroscopy was the method of choice for the diagnosis of esophageal and GEJ cancer [14]. Due to technical improvements in endoscopic as well as cross-sectional imaging, it is now an adjunct method for certain situations, like detection of esophago-tracheal fistula or postoperative assessment [15]. Endoscopy is more accurate and, although more invasive, the possibility to perform a biopsy puts it in the first line of workup for suspect BC [7]. Patients with lower grade dysphagia, or other less-specific symptoms, will eventually undergo a swallowing study and thus a potential lesion could be detected using this method. In the Appropriateness Criteria of the American College of Radiology (ACR), it is recommended to consider a barium swallow study as an initial examination in patients with dysphagia [16]. Especially in elderly, frail patients, fluoroscopy is used quite often since it is less invasive and it is a suitable first test for an initial workup. In cases of endoscopically non-passable strictures, fluoroscopy with barium swallow might help to identify the length of the stenosis [14], an example is shown in Fig. 11.1. However, before surgical or radio-oncological intervention, a CT scan needs to be performed anyway, which would be superior in demonstrating the extent of disease.

Fluoroscopy with oral contrast using a nonionic contrast agent has its role in the diagnosis of postoperative anastomotic leakage and to assess fistula [15] and is therefore performed routinely in many institutions, including ours.

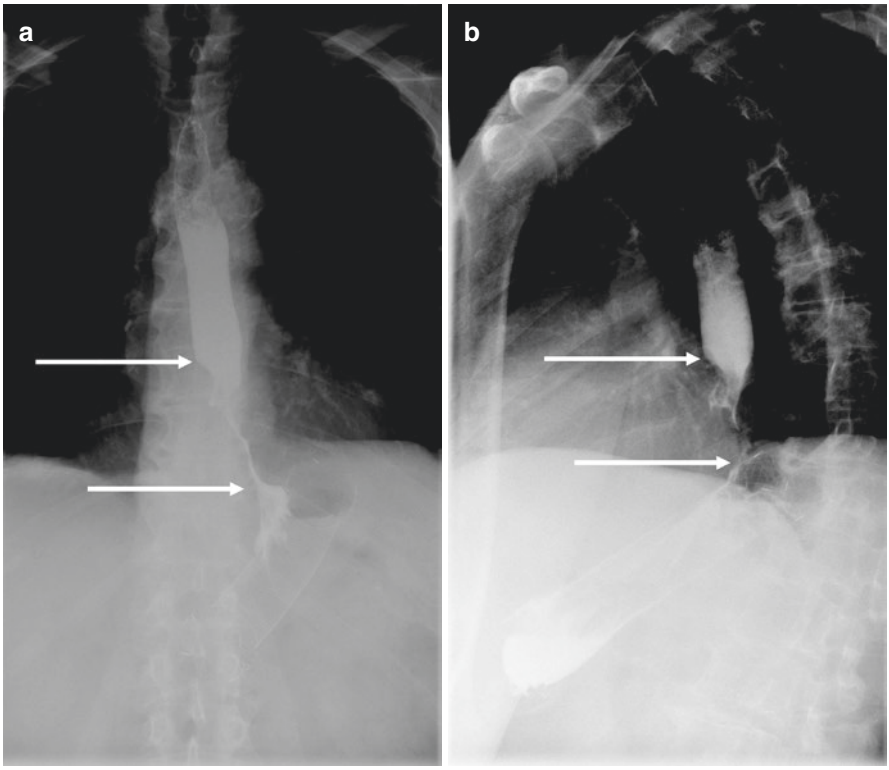


Fig. 11.1 Swallow study in a patient with known distal esophageal adenocarcinoma under current chemoradiotherapy. A stent had been placed prior to radiotherapy due to absolute dysphagia. The patient had again developed dysphagia during therapy, therefore this study was ordered. (**a**) Coronal, (**b**) sagittal view after oral ingestion of non-ionic contrast material. Note a high-grade stenosing tumor in the distal esophagus, extending into the gastro-esophageal junction. The arrows indicate the craniocaudal extension of the lesion. A dislocated esophageal stent is appreciated in the stomach. There is some degree of passage of the liquid contrast material across the stenosing tumor

11.4 Ultrasound

The only role of transabdominal ultrasound in BC is to screen for the presence of liver metastases [17]. Its diagnostic accuracy is, however, inferior to CT and MRI, especially in obese patients or patients who have severe steatosis [18]. It is therefore not recommended to solely rely on a negative ultrasound examination to rule out liver involvement. Cervical ultrasound can be used to better assess nodal involvement in the neck, if the findings on CT are equivocal [19]. The role of endoscopic ultrasound is quite a different one and will be discussed in the respective chapter. Of note, it is the method to best perform locoregional staging (tumor and nodal status) with a sensitivity and specificity to correctly assess the T-category of 81–92% and 94–97%, respectively [20]. The sensitivity of N-staging is in the range of 85% and can even be increased with the use of fine-needle aspiration [20]. This is significantly higher than

pooled accuracy analyses for CT and FDG-PET, which have been reported to be around 65–69% [21]. The diagnostic accuracy for locoregional staging is significantly lower after neoadjuvant therapy [22].

11.5 Computed Tomography

Computed tomography is the method of choice for locoregional and distant staging of BC. Its broad availability, uncomplicated application, and rapid delivery of the results render it the optimal method to assess whether a patient might be a surgical candidate, requires preoperative neoadjuvant therapy, or if palliative therapy would be appropriate [23]. Although most of this information can be retrieved by any standard CT examination, the use of an appropriate scanning technique facilitates the correct staging, with only little additional effort.

11.6 Hydro-CT for Staging of BC

In the physiological state, the lumen of the esophagus and gastro-esophageal junction is collapsed, hence, visualization of neoplastic processes that affect the wall can hardly be performed, an issue, that is well known from other gastrointestinal imaging techniques like CT-colonography [24]. Therefore, several approaches to distend the esophageal lumen have been reported and are currently used in clinical practice.

The use of oral effervescent powder is very well tolerated and leads to an accumulation of air in the upper GI tract, increasing the tissue contrast between the bowel wall and the lumen [25]. In our experience, though, not all patients can contain the gas within the upper GI tract and that during the CT examination, the luminal distension is often already lost. A different option is to use liquid positive or negative contrast materials for luminal distension. Although regularly used for fluoroscopy, the use of positive oral contrast is counterproductive in the CT staging of BC, since the mucosa will be obscured by the strong positive contrast and in practice, a correct staging will not be possible [23]. In our institution, we do however use positive oral contrast for the workup of postoperative complications. The best way, in our practice, which is also reflected by results in the literature, is to use plain water as a negative oral contrast for CT staging of BC [8]. If instructed correctly, even patients with dysphagia can ingest the amount of water required to provide the distension for optimal luminal visualization of BC. We ask patients to drink 1–1.5L of water before the examination, with the last sip of fluid ingested on the scanner table. This is usually tolerated well with no observed side effects in our experience. Patients with absolute dysphagia and advanced tumors might not require luminal distension because the tumor bulk is visualized on the CT image nevertheless. In those locally advanced patients, it is more important to identify invasion into adjacent structures, than to decide, whether a tumor might be of low or intermediate T-stage. Using this technique, a correct T-staging can be determined in 76% of patients [8]. For the CT examination, any modern-area scanner type, ideally a 64-row multidetector CT or better, can be used. In most CT scanners used today, the scan of the chest and abdomen can be performed within a few seconds, obviating

the need for relaxants like butylscopolamine or glucagon. In any patient with upper gastrointestinal carcinoma and especially in BC, we perform an arterial phase starting from the neck, covering the chest and upper abdomen [8]. First, this extended range is used in order to include the entire esophagus in the scan range, since second carcinomas have been described quite prevalently [10], although this is rarely encountered in BC. Second, the head and neck region is the area most commonly affected by unexpected metastases with 42% in a systematic review [26], interestingly quite commonly associated to distal esophageal adenocarcinoma. In this case, neck involvement would equal distant metastatic disease, completely changing the management of the patient. Third, scanning of the chest is required to rule out lung metastases and to display the lymph node regions along the esophagus and mediastinum. Fourth, the liver is covered in the arterial phase, giving better visualization for hypervascular metastases, which can occur in BC. Lastly, the mucosal enhancement is best seen in the arterial phase and even layers of the intact GI wall can be differentiated by this technique [8]. We then add a portal venous phase of the abdomen and pelvis, in order to stage for locoregional and distant metastases, especially liver metastases and peritoneal carcinomatosis. The efficacy of this is discussed in the following chapters. In our institution, we combine the Hydro-CT technique with an [18F]-FDG PET scan, which will be described in a later paragraph.

11.7 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is nowadays a standard methodology in the staging of any gastrointestinal malignancy. The excellent tissue contrast and the variable use of contrast agents, as well as functional imaging techniques like dynamic contrast-enhanced (DCE) imaging, diffusion-weighted imaging (DWI), and spectroscopy, do not only allow optimal assessment of liver involvement but are also increasingly used in the characterization of the primary tumor. In the case of BC, the use of MRI in locoregional staging is limited since motion artifacts caused by swallowing and bowel movements limit the optimal delineation of the GEJ and distal esophagus. In some studies, though, a comparable accuracy to MDCT in TNM staging, especially in the gastroesophageal junction, has been reported [27, 28]. Multiparametric MRI has been reported to be useful in determining features of tumor biology like aggressive local growth or a propensity to develop distant metastases [29]. However, this is currently matter of research and is not used in clinical practice. One application with potential use in the routine assessment of BC is the superior prediction of lymph node metastases by MRI techniques like DWI. With conventional staging methods, even in patients that are staged T2/3 N0, there is a high likelihood of nodal disease upon surgery, reaching 60% in one study [30]. Using MRI with DWI, the discrimination of malignant versus benign lymph nodes can be improved, yet the sensitivity and specificity are still quite poor, given that they are quite important features of tumor biology [31].

For the detection of liver metastases, MRI is the gold standard imaging technique. Due to the frequent occurrence of liver metastases and its therapeutic implication, we use it quite frequently in patients, who are potential candidates for curative surgery and who have equivocal liver lesions (Fig. 11.2). With the use of

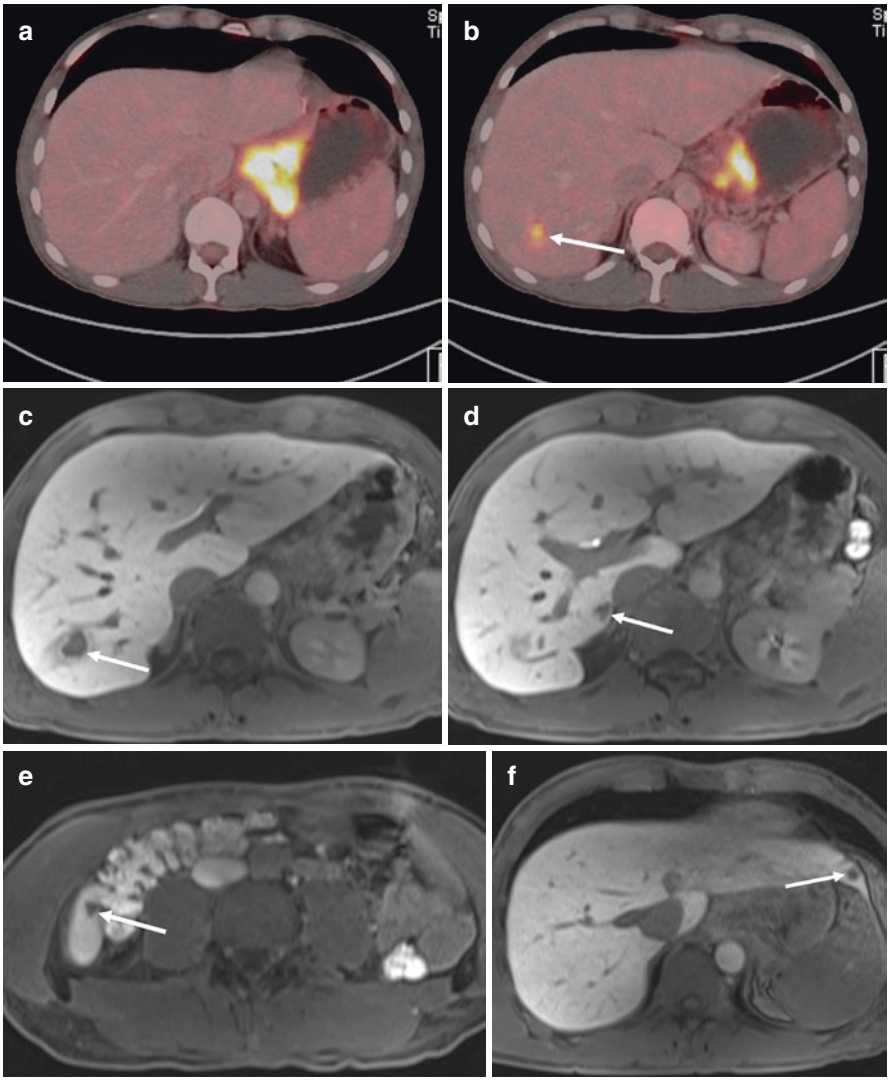


Fig. 11.2 Added value of liver MRI in a young patient with a bulky Barrett carcinoma. A 35-year-old male patient with a bulky Barrett carcinoma (clinical stage T4a, node positive), underwent [18F]-FDG-PET/CT for staging. Apart from the primary tumor (**a**), one metastasis with pathologic FDG uptake is appreciated in Segment VII of the liver (**b**, arrow). In the backlight of the patient age and the solitary metastatic site on [18F]-FDG-PET/CT, a treatment plan to resect the primary tumor with intraoperative ablation of the liver metastasis after induction therapy was created. For further workup, a liver MRI with application of a hepatocyte specific contrast agent was conducted (**c**–**f**: Gadoxetic acid—enhanced MRI, axial T1-gradient echo sequence with fat saturation in the hepatobiliary phase). In addition to the already known metastasis in Segment VII (**c**), three more metastases were detected in Segments V (**d**), VI (**e**) and III (**f**), indicated by arrows. The treatment plan was abandoned and palliative chemotherapy was initiated

hepatocyte-specific contrast agents, the diagnosis of liver metastases can be made with great confidence, even in lesions smaller than 1 cm [32]. Due to its typical imaging appearance, this diagnosis can often be made noninvasively, with a high sensitivity and specificity, and without the need of a biopsy [33].

11.8 Hybrid Techniques: PET/CT and PET/MRI

The advent of the combination of nuclear imaging techniques like positron emission tomography (PET) with CT has led to an improved diagnosis and management of patients with esophageal carcinoma and BC (Fig. 11.3). Similar to lung cancer and

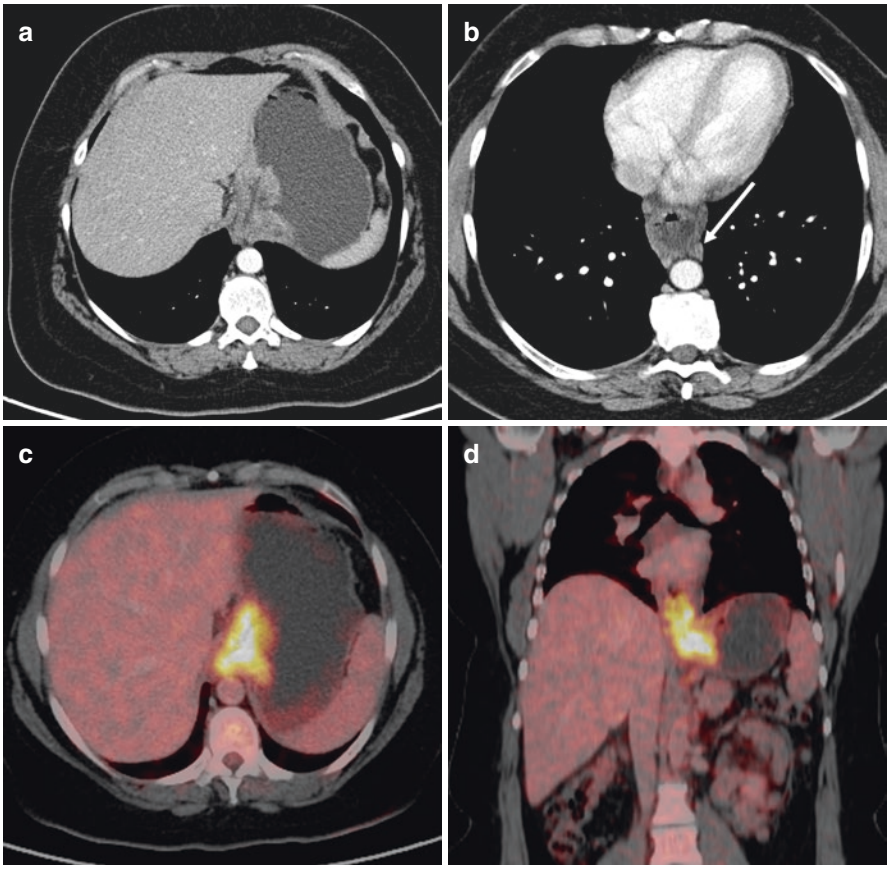
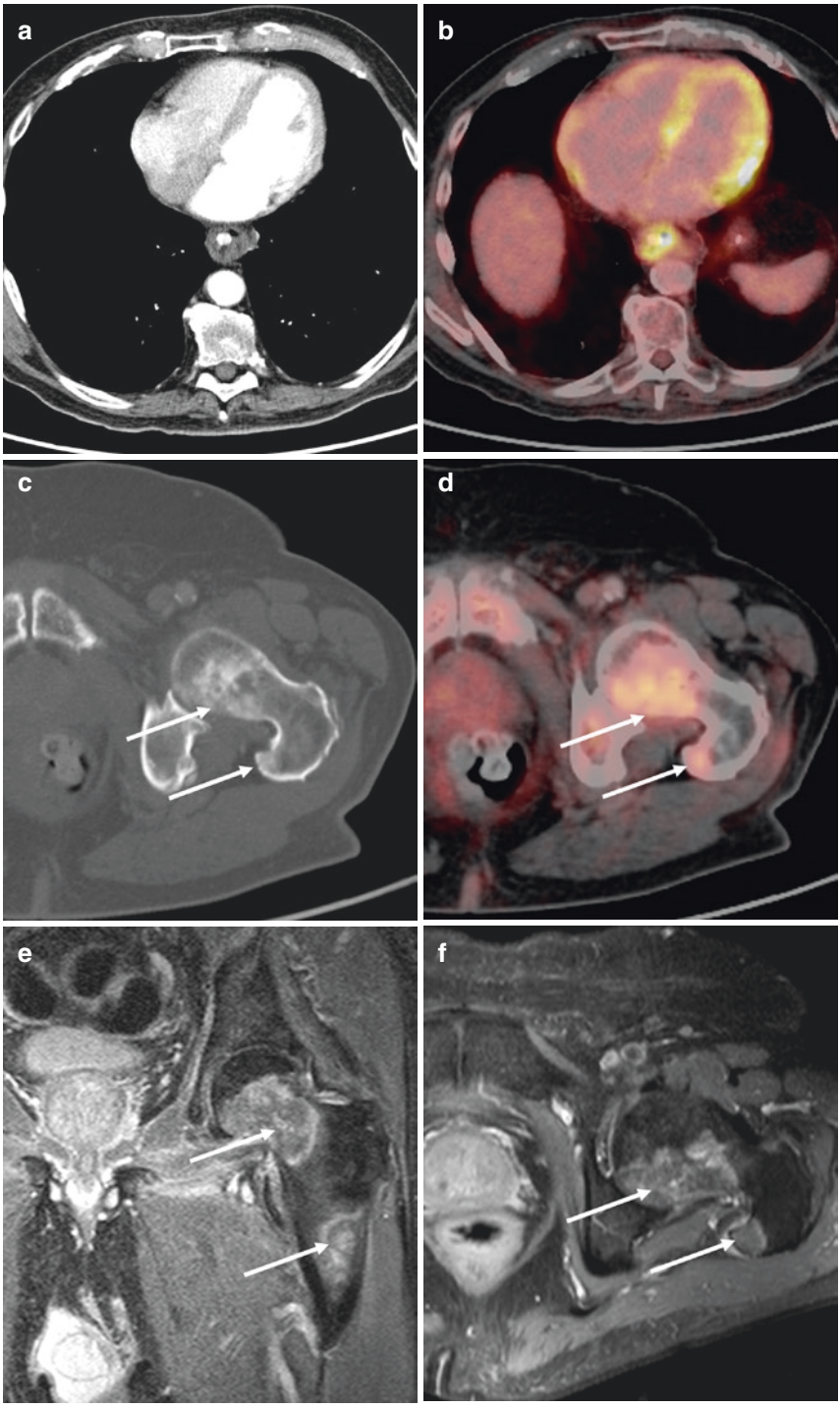


Fig. 11.3 Staging of Barrett carcinoma using [18F]-FDG-PET/CT. (**a**) Axial contrast-enhanced CT scan of the upper abdomen in the arterial phase. A bulky mass is appreciated in the region of the gastro-esophageal junction. It seems not to invade into adjacent structures, yet all layers of the intestinal wall seem to be affected (cT3). (**b**) Axial contrast-enhanced CT scan of the upper abdomen in the arterial phase. Further cranial, several peri-esophageal lymph nodes are appreciated in the lower mediastinum with suspicious radiomorphological characteristics (cN positive, arrow). (**c**, **d**) Fused [18F]-FDG PET scan using both input from [18F]-FDG-PET and contrast-enhanced CT in the axial (**c**) and coronal (**d**) view. A vivid FDG uptake is appreciated in the entire mass, enabling for optimal assessment of craniocaudal extension, identification of locoregional and distant metastases as well as other primary tumors in the upper gastrointestintal tract

its ability to develop metastases anywhere in the body (in contrast to, e.g., colorectal cancer, which usually affects liver and lung first), the chance to miss metastases on a standard CT of the chest and abdomen is quite high – given the importance of this finding in BC. It has been shown on several occasions that the use of PET/CT can overcome this limitation, detecting metastases in 13–15% of patients who were initially staged M0 [34], with change of clinical management in 38–40% of cases [11, 12] (Figs. 11.4 and 11.5). Even in patients, who were initially staged cM0 using CT, PET/CT changed the management in 23% of patients, 20% due to confirmation of either questionable or occult metastases and 3% due to unexpected findings and second cancers [35]. It has also been shown that this investigation is cost-effective, given the quite high cost of understaging and hence overtreating patients in this disease. The routine use of [18F]-FDG PET/CT for staging of BC is therefore also recommended in surgical guidelines [36]. For the detection of peritoneal carcinomatosis, even the best available imaging methods remain suboptimal. The overall sensitivity remains around 75%, especially nodules smaller than 5 mm pose a technical challenge in detection and interpretation with sensitivities reported around 43% [37]. Staging laparoscopy can help in these situations to increase the detection rate of yet unrecognized carcinomatosis [38], preventing futile surgeries in patients who will develop recurrence rapidly after resection. This is especially true for BC and GEJ cancers, since tumors above the hiatus are less frequently prone to develop peritoneal carcinomatosis [35, 38].

From a technical aspect, many institutions perform [18F]-FDG PET/CT as a PET examination with a low-dose, non-contrast CT for attenuation correction. This is ideal from the nuclear medicine perspective because PET and CT can be performed without any intravenous contrast application and without the need to read the CT scans separately. Especially in the perioperative setting, though, a detailed anatomical visualization is required, which can only be realized with a regular contrast-enhanced CT scan [39] (example of a potential medical pitfall is illustrated in Fig. 11.6). The feasibility to combine both techniques in one examination makes [18F]-FDG PET/CT quite an attractive modality for a one-stop examination in the

Fig. 11.4 Value of [18F]-FDG-PET/CT in the detection of distant metastases. A 74-year-old male patient with distal esophageal adenocarcinoma, who had completed radiochemotherapy, underwent restaging with [18F]-FDG-PET/CT (**a**, **b**) with the intent to proceed to surgical resection. The tumor in the distal esophagus remained stable, with still relevant [18F]-FDG uptake, however, no clear progression was noted and the locoregional tumor stage was interpreted as stable. A mixed sclerotic/lytic lesion in the left femoral neck and trochanter minor region was appreciated (**c**, CT with bone window), with mild FDG uptake (**d**, fused FDG-PET/CT). On the pretherapeutic [18F]-FDG-PET/CT, this region was unremarkable. The suspicion of new bone metastases was raised and the patient underwent an MRI of this region. (**e**) Coronal T2-weighted sequence with fat suppression (STIR) and (**f**) axial T1-weighted sequence with fat suppression, after the application of gadolinium. On both sequences, a lesion with pathologic contrast enhancement is seen in the femoral neck replacing the bone marrow, extending to the lesser trochanter. A second lesion, with similar MR features, is seen in the subtrochanteric region, arrows. With these images, the suspicion of bone metastases was confirmed and the patient continued on palliative medical treatment, no surgical resection was performed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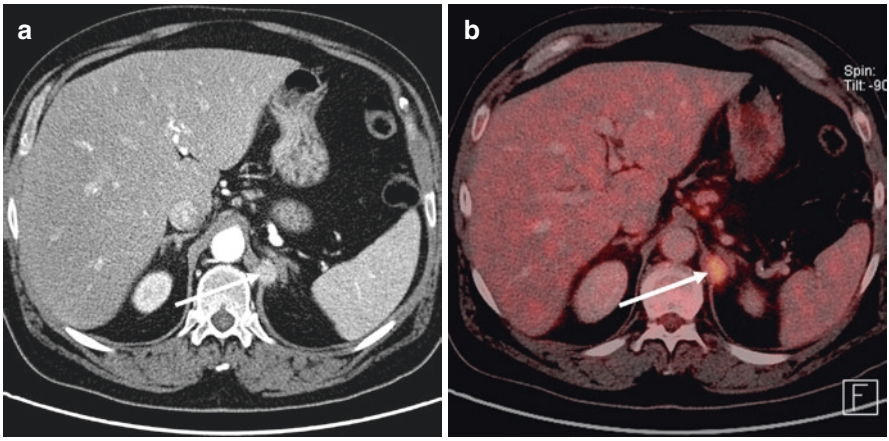

Fig. 11.5 Value of [18F]-FDG-PET/CT in the characterization of a potential distant metastasis. A 53-year-old male patient who had just completed neoadjuvant chemotherapy for locally advanced Barrett carcinoma. On the restaging [18F]-FDG-PET/CT, a new retroperitoneal lesion (**a**) is seen adjacent to the left adrenal gland. Pathologic FDG uptake (**b**) confirms this as a new distant lymph node metastasis (alternatively, peritoneal implant), which changed the clinical stage to stage IV. No surgical resection was performed, the patient continued on palliative medical therapy

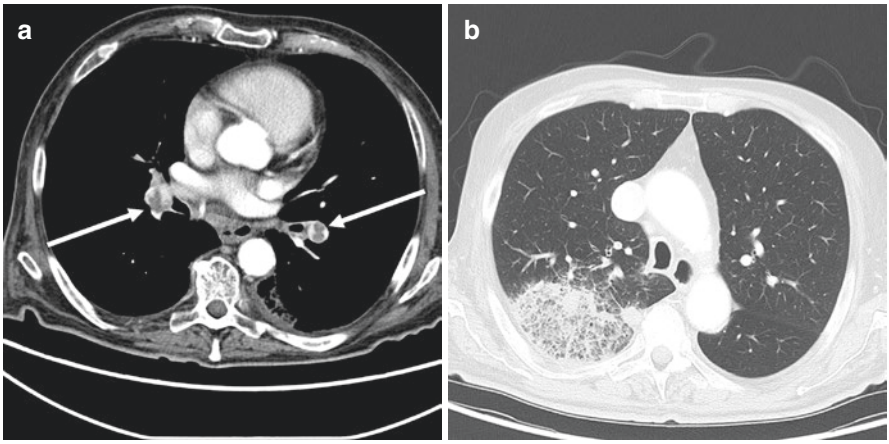

Fig. 11.6 Medical complication during chemoradiotherapy. A 64-year-old male patient who underwent neoadjuvant chemoradiotherapy for resectable distal esophageal adenocarcinoma. During the last days of treatment, patient reported dyspnea, a low-grade fever and increased fatigue. Antibiotic therapy was initiated for a suspected pneumonic infiltrate visible on a chest X-ray. The symptoms decreased only to a moderate degree, until an [18F]-FDG-PET/CT was scheduled for restaging. Apart from the oncologic assessment, bilateral pulmonary embolism is appreciated in all segmental arteries (**a**). In the right lower lobe, pulmonary infarction is seen (**b**), which was mistaken for pneumonia on the chest X-ray. Surgery was postponed for 6 weeks, the patient recovered well under oral anticoagulation and was resected without further pulmonary complications. This case illustrates, why staging or restaging using [18F]-FDG-PET/CT should always include a contrast-enhanced CT-scan, since sometimes relevant ancillary findings might be present

staging of BC. Therefore, from our perspective, all patients that are potential candidates for a surgical resection should receive an [18F]-FDG PET/CT with a dedicated CT protocol using intravenous contrast as described above [2].

PET/MRI has been recently introduced for oncologic imaging and is frequently used at our institution for various indications other than staging of BC. For the present, it is mainly used in pediatric patients, in patients with lymphoma and prostate cancer, but there is a potential use for gastrointestinal applications and in BC [40] as well (Fig. 11.7). Unfortunately, this new method is not distributed well enough yet to be recommended in diagnostic pathways.

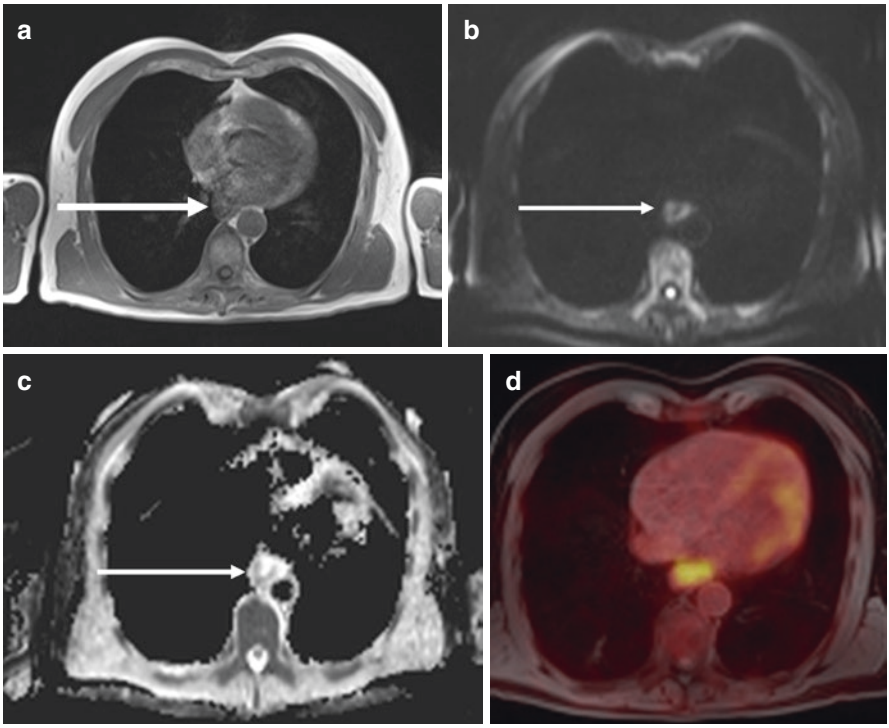

Fig. 11.7 [18F]-FDG-PET/MRI imaging of distal esophageal adenocarcinoma. (**a**) Axial T1-weighted gradient-echo sequence without fat suppression (T1-VIBE_DIXON sequence). The lesion in the distal esophagus is hardly appreciated. Note respiratory and cardiovascular motion artefacts. (**b**, **c**) Diffusion-weighted imaging. Using this technique, areas of restricted Brownian motion of hydrogen protons, which occurs for instance in dense tumor tissue, can be displayed. (**b**) shows the image with a so-called high *b*-value, whereas (**c**), the ADC (apparent diffusion coefficient) map, displays the relative differences in diffusability across tissues. Dark signal in this case means restricted diffusion, or dense tumor tissue. (**d**) On the fused [18F]-FDG-PET/MRI image, the lesion is clearly demonstrated in this region with a strong uptake of [18F]-FDG. Note, that [18F]-FDG-PET/MRI is currently only used for research purposes at academic institutions, since is not available yet for broad clinical applications

11.9 Restaging After Neoadjuvant Therapy

In locally advanced BC, similar to EC, it is now routine to perform neoadjuvant chemotherapy or chemoradiotherapy, according to results of phase III trials demonstrating superior survival compared to patients without neoadjuvant therapy [41–43]. The potential use is not only to downstage patients and sometimes to improve resectability in bulky tumors, but also to identify patients with progression on therapy, who quickly develop metastatic disease and who will not benefit from a surgical resection. Furthermore, there have been promising data already some years ago, which addressed early response assessment in BC treated with neoadjuvant chemotherapy, with the goal to identify patients with very good or very poor response (MUNICON I trial [44]). In that respective trial, it was shown that within two cycles of chemotherapy it could be determined, whether a patient would have good response to therapy and hence a better survival, compared to a patient with poor response, expressed by changes in metabolic activity on an [18F]-FDG PET scan. In the follow-up study by the same group (MUNICON II trial), this concept was expanded so that initially nonresponding patients would receive salvage chemoradiotherapy instead of chemotherapy. The primary end point, to increase the R0 resection rate, was not met in this study [45]. The preliminary results of a randomized study not yet published (CALBG 80803) indicate a promising strategy of assessing early response after a short-term course of induction therapy (two different regimens), followed by CRT and either continuation on the same regimen in responders or switch to the respective other regimen in nonresponders. With this concept of adaptive management based on early response assessment, a good histologic response in initial nonresponders was achieved, and survival data available so far also appear to be improved.

In our institution, we perform response assessment using an [18F]-FDG PET/CT [13, 46, 47], with a diagnostic contrast-enhanced CT scan. PET is mainly used to assess for the possibility of a complete response. However, there is a considerable rate of false-negative tumors on FDG-PET after treatment, so potentially, the treatment success might be overestimated. Furthermore, radiation esophagitis can hinder the proper interpretation of FDG uptake, since a small residual lesion might be lost in the strong background of inflammatory glucose uptake (Fig. 11.8). Therefore, response assessment should be combined with a diagnostic CT scan, since it has been shown recently that only the combination of [18F]-FDG PET and contrast-enhanced CT is superior in identifying patients with complete or incomplete response, allowing to perform a clinical TNM staging after therapy [48].

11.10 Role of Imaging in Follow-Up and Detection of Recurrence

Currently, there are no data available, that adhering to a strict follow-up protocol for patients after esophagectomy is advisable, since there are no studies demonstrating a survival benefit if recurrence is detected early. Only in patients with complete response to neoadjuvant therapy, who are managed with observational management

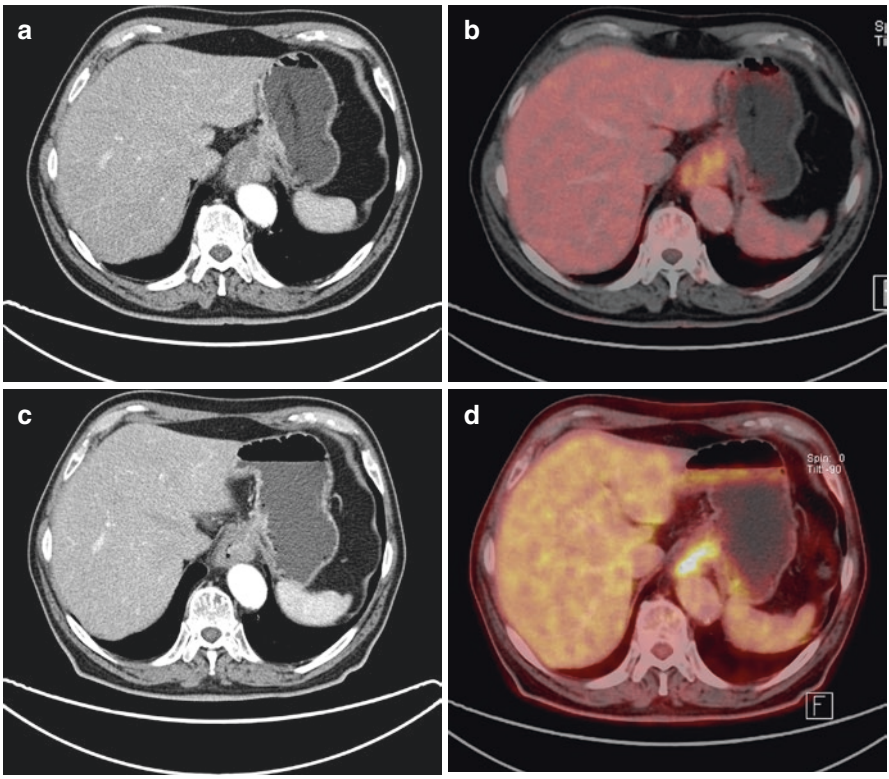

Fig. 11.8 Pitfall in Restaging of Barrett carcinoma using [18F]-FDG-PET/CT. A 76 year-old male patient with adenocarcinoma of the gastroesophageal junction (GEJ). (**a**, **b**) shows an axial [18F]-FDG-PET/CT of the tumor prior to treatment (**a**, contrast-enhanced CT scan, **b**, fused FDG-PET and CT image). A bulky mass is appreciated in the area of the distal esophagus and gastro-esophageal junction, with moderate FDG uptake. The clinical staging was cT3, N+, M0. Chemoradiotherapy was applied and restaging using [18F]-FDG-PET/CT was again applied 6 weeks after end of therapy (**c**, **d**). The lesion at the GEJ is almost unchanged in size, with probably a moderate decrease of contrast enhancement. In contrast, there is vivid FDG uptake throughout the lesion. The therapy assessment was deemed unchanged, stable. The final histopathologic result after esophagectomy was ypT0, N0 (0/34), L0, V0, Pn0, R0, tumor regression grade (TRG) I according to Mandard, equal to a complete pathologic response. A marked inflammatory reaction was reported in the entire specimen, compatible with radiation esophagitis

and an option of salvage surgery in case of recurrence, regular CT follow-up examinations might be viable [49]. This is, however, more often the case in esophageal squamous cell carcinoma.

11.11 Outlook

In the future, exciting new features will become relevant in the staging and restaging of BC using radiological methods. Using machine learning, deep learning algorithms, and convolutional neuronal networks, the characterization and interpretation

of EC and BC will be improved, adding more features of tumor biology into the standard diagnostic information. With this information, one day it might be possible to identify beforehand, whether a patient will respond to a certain neoadjuvant therapy and how the clinical course of that patient will be. The goal would be to robustly identify patients with complete pathological response, who might be candidates for a nonoperative approach, similar to what is currently being explored in rectal cancer. Working together tightly with all clinical specialties involved in this devastating disease, an improvement of outcome for patients with BC will not only be a possibility, but will become reality.

Acknowledgments I would like to thank Prof. Dr. Ahmed Ba-Ssalamah and Prof. Dr. Alexander Haug for sharing their expertise and for their continuous effort to optimize imaging in this difficult disease entity.

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Surgical Treatment of Esophageal Adenocarcinoma

12

Philipp Gehwolf, Heinz Wykypiel, and Dietmar Öfner

12.1 Multimodal Approach to Resectable Esophageal Adenocarcinoma

Surgery is the primary curative modality for adenocarcinoma of the esophagus and EGJ cancers. However, long-term outcomes are not satisfactory with resection alone, even if microscopically complete (R0) [1, 2]. This poor long-term outcome has prompted an evaluation of neoadjuvant (preoperative), perioperative, and adjuvant (postoperative) combined modality therapies. Significant progress has been made in the past two decades in the multimodality treatment of locally advanced nonmetastatic esophageal cancer. Patients with esophageal adenocarcinoma have been included in many of the trials examining the benefit of perioperative chemotherapy for gastric cancer, and this approach is widely used. To date, the best approach to multimodality therapy is not established. Areas of debate include the benefits of perioperative chemotherapy versus preoperative chemoradiotherapy versus initial surgery followed by postoperative chemoradiotherapy or chemotherapy, the specific drug regimen and radiation dose/schedule to be used both for chemotherapy alone and neoadjuvant chemoradiotherapy as well as the surgical approach [2, 3] (Table 12.1).

Combined modality therapy rather than surgery alone is recommended in patients with cT3 or higher or node-positive esophageal and EGJ adenocarcinoma. In general, a doublet rather than a single-agent chemotherapy with option for a concurrent regimen is advised. For a combined chemoradiotherapy, a standard dose of radiation

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_12

Table 12.1 List of clinical trials establishing a multimodal therapy concept (summary) in esophageal cancer treatment

Author	Year	Title	Journal	Number	N Arm 1	n Arm 2	HR	Follow up	Comment
Mcdonald et al.	2001	Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction	N Engl J Med	556	275 surg	281 RCTx + surg	1.36 RCTx + surg	60	US intergroup trial 0116
Cunningham et al.	2006	Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer	N Engl J Med	503	253 surg	250 CTx + surg	0.74 CTx + surg	49	MAGIC
Stahl et al.	2009	Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction	J. Clin Oncol	119	CTx + surg	RCTx + surg	0.67 RCTx + surg ($p = 0.7$)	46	POET
Medical Research Council Oesophageal Cancer Working Group	2002	Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial	Lancet	802	402 surg	400 CTx + surg	0.79 CTx + surg	37	(MRC) OEO2
Kelsen et al.	1998	Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer	N Engl J Med	440	227 surg	213 CTx + surg	$p = 0.53$	55.4	US Intergroup trial 0113

Ychou et al.	2011	Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial	J Clin Oncol	224	111 surg	113 CTx + surg	0.69 CTx + surg ($p = 0.02$)	68	FNLCC/ FFCD
Schumacher et al.	2010	Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954	J Clin Oncol	144 stopped	72	72	0.84 ($p = 0.466$)	53	EORTC trial 40954
Al-Batran et al.	2016	Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial	Lancet Oncol	300	152 (ECF/ ECX + surg	148 (FLOT) + surg	50 vs. 35 months median surv (FLOT)	43	FLOT4-AIO
van Hagen et al.	2012	Preoperative chemoradiotherapy for esophageal or junctional cancer	N Engl J Med	366	188 surg	178 RCTx + surg	0.657 RCTx + surg ($p = 0.003$)		CROSS

for patients treated with concurrent chemotherapy between 41 and 60 Gy is applied regardless of the specific chemotherapy regimen used.

In patients with cT1-2N0 tumors, the benefit of neoadjuvant therapy is less clear. The use of induction therapy for T2N0 tumors is somewhat controversial, as both clinical understaging and overstaging is common. Clinical trials demonstrated a significant benefit in survival for neoadjuvat concurrent chemoradiotherapy versus surgery alone (Table 12.1; the POET trial, the CROSS trial, the Irish trial, and CALGB9781) [4–7]. Non-randomized trials, directly comparing neoadjuvant chemotherapy with chemoradiotherapy, showed better histological response and higher rates of margin negative resections (R0) in the chemoradiotherapy group, but none of them demonstrated that these benefits translate into an improved survival. However, choosing perioperative chemotherapy as a reasonable approach, a docetaxel-based triplet therapy, is currently recommended (FLOT). Neither neoadjuvant chemotherapy nor chemoradiotherapy increase the risk of postoperative mortality or morbidity in most of the trials. Taken together, there is no clear recommendation for a specific treatment regimen particularly due to lack of trials that focus on EGJ and trials including different histologic forms and gastric as well as esophageal cancers.

The decision of a neoadjuvant/perioperative regimen remains tumor-board advised and should be guided by the patients' clinical condition. However, complete surgical resection is a prerequisite for cure.

12.2 Timing of Surgery Following Neoadjuvant Therapy

The optimal timing between completion of neoadjuvant chemoradiotherapy and resection is not established. The typical interval, 4–7 weeks, is arbitrary, with the intent of allowing resolution of acute inflammation and allowing for tumor regression while minimizing the chronic fibrotic changes in the surgical field. Most tumors regress slowly after chemoradiotherapy because one of the ways in which the cells die is through mitotic death that occurs only during cell division. Increasing the interval between treatment completion and resection may allow the tumor to continue to regress, thereby improving resectability, and increase the chance of observing a pathological complete response (pCR). Studies have shown that pCRs in patients undergoing trimodally treatment for esophageal cancer predict decreased local and distant recurrence and improved survival [8–10].

The optimal time for surgery following neoadjuvant chemotherapy may be 3–6 weeks following completion of chemotherapy. The optimal time for surgery following neoadjuvant chemoradiotherapy may be 6–12 weeks following the last day of radiotherapy [11].

12.3 Utility of Postinduction Therapy [^{18}F]-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) Scans

The idea of a postinduction therapy [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) is to determinate patients with good or bad response to an induction therapy and delineate patients who may benefit from an early operation or patients who may not benefit from esophagectomy at all. Postinduction therapy FDG-PET may provide useful information about metabolic response. However, a systematic review on this topic (including the MUNICON II trial) concluded that the available data are too contradictory to consider a postinduction FEG-PET as a standard approach [12]. Furthermore, there is currently no evidence regarding tailoring the therapy components in case of a non-responder.

However, postinduction therapy FDG-PET, 4 weeks after completion of induction therapy, is endorsed as a method to assess distant metastatic disease and may serve to preclude those patients from surgery [13]. FDG-PET combined with a high-dose contrast CT imaging detects distant metastasis in approximately 8% of patients following induction chemotherapy. In many cases, the metastasis is localized in skeletal muscle, subcutaneous tissue, brain, or thyroid gland [14].

For patients undergoing chemoradiotherapy for potentially resectable disease who have a complete clinical response, the necessity of subsequent surgery is currently under debate, large randomized multicenter trials are ongoing [15–17]. Nevertheless, the problem is early detection of recurrent disease (endoscopy, ultrasound-guided biopsy of suspect lymph nodes, CT, and PET). Of note, a clear definition of chemoradiotherapy response is not established [18].

12.4 Gastroesophageal Junction Carcinoma

The lack of a clear definition of the esophagogastric junction (EGJ) and gastric cardia has contributed to difficulties in classification of these tumors and has hampered definition of the optimal multimodality strategy [19–22]. Of note, it remains even unclear as to whether or how histology should dictate the therapeutic approach.

In the most recent AJCC/UICC staging system (2017, eighth edition), tumors involving the esophagealgastric junction (EGJ) with the tumor epicenter no more than 2 cm into the proximal stomach are staged as esophageal cancer. This recent staging system may simplify the differentiation of adenocarcinoma of the EGJ into esophageal cancer and gastric cancer without a subclassification into adenocarcinoma of the esophageal junction I–III (AEG I–III; Siewert-Hölscher-classification) [23]. However, in the current international guidelines (NCCN, AWMF), the carcinoma of the esophageal-gastric junction (EGJ) is still divided

into adenocarcinoma of the esophageal-gastric junction (AEG I–III; Siewert I–III). In AEG I tumors, a classic esophagectomy is common sense. For AEG II tumors, there is more room for discussion: gastrectomy with distal esophagectomy as well as a transthoracic distal esophagectomy or a transhiatal esophagectomy are currently performed to determine tumor localization, patient's performance, and surgeons experience [13, 24]. In AEG III tumors, a gastrectomy with partial transhiatal resection of the esophagus is commonly performed (treatment of gastric cancer) [13, 24].

12.5 Management of Superficial Esophageal Cancer

Lesions that do not exceed the mucosal layer (T1a), remaining within the mucosal epithelium or the lamina propria mucosae, are extremely rarely associated with lymph node metastasis. Therefore, complete endoscopic mucosal resection (EMR) is a sufficiently radical treatment. Lesions reaching the muscularis mucosae (m3) or slightly infiltrating the submucosa (up to 200 µm, T1b-sm1) are amenable to mucosal resection, but may have a risk of lymph node metastasis up to 13%. Therefore, these cases represent relative indications. Furthermore, lesions invading deeper (more than 200 µm) into the submucosa (T1b-sm2) are associated with metastasis (about 50%) and should be treated in the same manner as advanced carcinomas. Regarding the limitations of endoscopic ultrasound (poor overall accuracy of around 65%), pathology result from the EMR can be used to guide the final decision as to whether endoscopic therapy alone is sufficient or if surgery should be recommended thereafter. A comparison of the depth of invasion and the risk of lymph node metastasis is shown in Table 12.2 [25–27].

EMR or esophageal submucosal dissection (ESD) covering three-fourths of the entire circumference is likely to be associated with postinterventional strictures, and therefore should be avoided.

Various complications, including bleeding, esophageal perforation, and cicatricle stenosis, have been reported in association with endoscopic resection. The need for prevention, prophylactic measures, and treatment of these complications should be well recognized.

Table 12.2 In esophageal adenocarcinoma, the risk of lymph node metastasis is depending on the depth of invasion [25–27]

TNM		Anatomy	Risk of N+ (%)
T1a	m1	Limited to the epithelial layer	0
	m2	Invades the lamina propria	0
	m3	Invades into but not through the muscularis mucosa	0–4
T1b	sm1	Penetrates the shallowest one-third of the submucosa	0–13
	sm2	Penetrates into the intermediate one-third of the submucosa	19–29
	sm3	Penetrates into the deepest one-third of the submucosa	54–67

12.6 Surgical Management of Resectable Esophageal Adenocarcinoma

Presently, there is no gold standard technique for the surgical approach in patients with esophageal adenocarcinoma. Surgical strategy and operation technique strongly depend on tumor location and surgeons' preference, width of the resection margin, extent of lymph node dissection, the organ and route used for reconstruction, multimodality therapy including adjuvant therapy, and salvage surgery following definitive (chemo-) radiotherapy.

For curative intent, a tumor-free resection margin and an extensive two-field (abdominal and mediastinal) lymphadenectomy is mandatory [28]. Precise staging and patient evaluation guide multidisciplinary management decisions, including surgical approach.

Surgery may be considered in patients with local tumors (T1–T3) and advanced tumor stage when curative resection is judged to be applicable (T4a). Surgery is far superior to definitive radiochemotherapy in terms of local recurrence [29]. However, surgery is not chosen as treatment when there are distant lymph node metastases or metastases to other organs.

12.6.1 Transhiatal Esophagectomy

Open and also laparoscopic transhiatal esophagectomy (THE; i.e., approach to the mediastinum from abdominally, through the diaphragm) is still under debate as an alternative with lower morbidity in some, but not in all studies [30–32]. With avoiding single lung ventilation, it was possibly considered a technique for rather unfit patients. Nevertheless, the extent of lymph node dissection in the upper mediastinum is very limited from the abdomen keeping in mind that even in adenocarcinoma of the distal esophagus, the rate of positive lymph nodes in the upper mediastinum was as high as 10% in some studies! Therefore, transhiatal resections might show worse oncologic outcomes.

12.6.2 Transthoracic Esophageal Resection

Two techniques with the anastomosis intrathoracically (Ivor-Lewis) or in the left neck (McKeown) are the most used ones [33, 34]. Both of them provide an en-bloc resection of the esophagus together with radical mediastinal lymph node dissection (two-field) under direct visualization [35]. The surgical approach is reserved to the preference of the surgeon. Originally, the McKeown and the Ivor-Lewis procedure were described as open procedures but during the last decade more and more hybrid and total minimal-invasive procedures were established. Some combine laparoscopy with thoracotomy while others prefer the thoracoscopic approach and perform the abdominal part of the operation by conventional midline laparotomy. The group preferring laparotomy argues that the mobilization of the gastric tube including a "Kocher's manoeuvre" can be done more easily in an open way and that the main

advantage of minimal-invasive esophagectomy (MIE) lies in a less-invasive thoracic part. On the other hand, those performing laparoscopy and thoracotomy rely on a "safer" performance of the intrathoracic anastomosis, e.g., with oversewing the circular-stapled anastomosis in order to avoid leaks. However, with enough expertise, both parts can be accomplished minimal invasively when a stepwise approach with proctoring from a high-volume reference center is available in order to fasten the learning curve. Complete MIE has shown to be better than open or hybrid minimally invasive esophagectomy (HMIE) in terms of postoperative pain and pulmonary complications with the same oncologic outcome in long term [36]. Moreover, a recent single-center analysis reported MIE as the superior procedure compared with open esophagectomy or hybrid procedures with respect to overall survival, peri-operative mortality, and severity of postoperative complications [37].

Oversewing and covering the anastomosis with a pedicled omentum seem to reduce the risk of anastomotic leaks [38] and can also be done during MIE with some experience in laparoscopic surgery (Fig. 12.1) [39–41].

Fellowships at high-volume centers, proctoring by experts and credentialing seems reasonable [42].

12.6.2.1 Reconstruction/Conduit

Due to its reliable vascularity, good outcomes, and relative simplicity with just one anastomosis, a tubularized gastric conduit is recommended as the first option (Fig. 12.2), while colon and jejunum (pediculated or free graft) may be indicated in special situations.

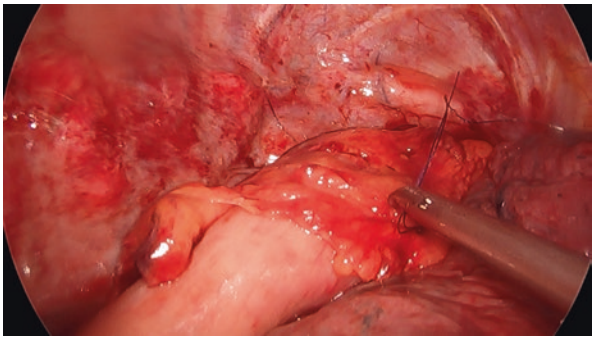

Fig. 12.1 Minimal-invasive esophagectomy (Ivor-Lewis): Intrathoracic view on the anastomosis in the right upper mediastinum (circular-stapled end-to-side esophagogastrostomy, covered with an omental flap)

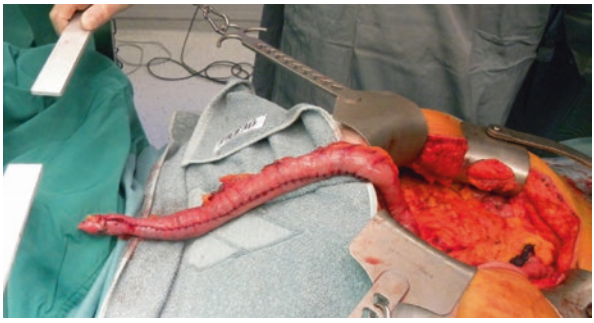

Fig. 12.2 The gastric tube as a conduit

12.6.2.2 Ivor-Lewis Transthoracic Esophagectomy

The transthoracic esophagectomy with intrathoracic anastomosis (Ivor-Lewis procedure) can be used to resect cancers in the lower third of the thoracic esophagus. However, it might not be the optimal approach for cancers located in the middle thoracic third because of a limitation of the proximal safety margin that can be achieved. This procedure combines a laparotomy or laparoscopy with a right thoracotomy or thoracoscopy and an intrathoracic esophagogastric anastomosis and permits direct visualization of the thoracic esophagus allowing an extend thoracic lymphadenectomy.

Disadvantages of the transthoracic esophagectomy include a 3–20% risk of severe bile reflux due to loss of the gastroesophageal anti-reflux mechanism, i.e., the lower esophageal sphincter (LES) [43, 44]. Therefore, antisecretoric drugs (e.g., PPI) and at least a 20–30° upright position of the upper part of the body are advised lifelong.

In comparison to the mainly mild consequences in cervical anastomosis, a leak occurring at the intrathoracic anastomosis has been associated with morbidity rates as high as 64% and increased mortality [45–50]. With current technique, mortality rates are substantially lower [51].

12.6.2.3 Modified Ivor-Lewis (Left-)Transthoracic Esophagectomy

A modification of the Ivor-Lewis transthoracic esophagectomy includes a left thoracoabdominal incision with a gastric pull-up and an esophagogastric anastomosis in the left chest [52]. This approach is most useful for tumors involving the gastroesophageal junction. Only one incision is required, but disadvantages include a high incidence of complications such as postoperative reflux and limitation of the proximal esophageal margin by the aortic arch. With MIE, the advantage of a single incision seems not so relevant anymore.

12.6.2.4 Tri-Incisional Esophagectomy (McKeown Procedure)

The tri-incisional esophagectomy combines the transhiatal and transthoracic approaches for total esophagectomy with an en-bloc thoracic lymphadenectomy and a cervical esophagogastric anastomosis [33, 53–56]. The tri-incisional technique allows for a complete two-field lymphadenectomy and a cervical esophagogastric anastomosis.

First, a right posterolateral thoracotomy or thoracoscopy is performed to assess resectability and exclude local invasion of contiguous structures. A subsequent en-bloc esophagectomy with mediastinal lymph node dissection is performed, including the right paratracheal, subcarinal, and periesophageal lymph nodes. Thereafter, a laparotomy or laparoscopy with extensive lymphadenectomy follows. The abdomen is explored to exclude metastatic disease, and a gastric conduit is created using the right gastroepiploic vessels for vascular supply and with inclusion of an omental fat pad for covering the anastomosis. A duodenal mobilization (Kocher's manoeuvre) helps to get more conduit length towards the neck.

Finally, a left neck exposure is preferred for the esophagogastric anastomosis since this approach reduces the risk of injury to the recurrent laryngeal nerve (RLN)

[43, 57–59]. However, the use of electric nerve stimulation for better visualization of the laryngeal recurrent nerve is advised (see below).

12.6.2.5 Cervical Versus Thoracic Anastomosis

When performed using a standardized technique, cervical and thoracic esophagogastric anastomoses are equally safe [60, 61]. At present, the choice of anastomotic location remains clinician dependent. A cervical anastomosis has a higher leak rate and the approach carries a risk of injury to the recurrent laryngeal nerve [60, 62, 63]. However, a neck anastomosis includes easier management of such an anastomotic leak, since the anatomic confines of the neck and thoracic inlet often limit the contamination of surrounding tissue thus often preventing pleural involvement of the infection. Moreover, it entails a lower incidence of reflux, more extensive proximal resection margin, and location of the anastomosis outside of the radiation field.

12.6.2.6 Circumferential Resection Margin

The prognostic role of a positive circumferential resection margin (CRM) for patients with esophageal cancer is under discussion, in part due to a lack of clear definition of a positive margin. Of note, the College of American Pathologists and the Royal College of Pathologists have different definitions for a positive CRM. Nevertheless, the overall 5-year mortality rates were higher for patients with a positive CRM compared with a negative CRM [64].

12.6.2.7 Extent of Lymphadenectomy

The appropriate extent of lymphadenectomy during esophageal cancer surgery is still a matter of discussion. The minimum number of lymph nodes that should be removed during potentially curative esophagectomy has not been established. However, as many regional lymph nodes as feasible should be removed, since more extensive lymphadenectomy has been associated with better survival [28, 65–69]. A greater number of retrieved lymph nodes generally reflect more accurate staging, a better technique which generally comes with more extensive resections.

In Europe and the United States, en-bloc resection of the mediastinal and upper abdominal lymph nodes is considered a standard component of transthoracic esophagectomy, for patients with adenocarcinoma of the esophagus [13, 24]. An even more extensive lymphadenectomy, three-field lymphadenectomy of the mediastinal, abdominal, and cervical nodes, is commonly practiced in some Asian countries for upper thoracic esophageal cancers, mainly squamous cell cancer [70]. While this approach increases the accuracy of staging, it is uncertain whether local control or survival is improved compared with two-field lymphadenectomy. However, if a lymph node dissection is not done, then lymph node sampling should be carried out to accurately stage the patient and to gauge the response to induction treatment in patients enrolled in trials using neoadjuvant therapy.

12.6.2.8 Hand-Sewn Versus Stapled Anastomosis

Anastomotic closure techniques include hand-sewn (single versus double layer), stapled (circular versus side-to-side linear), and hybrid linear stapled

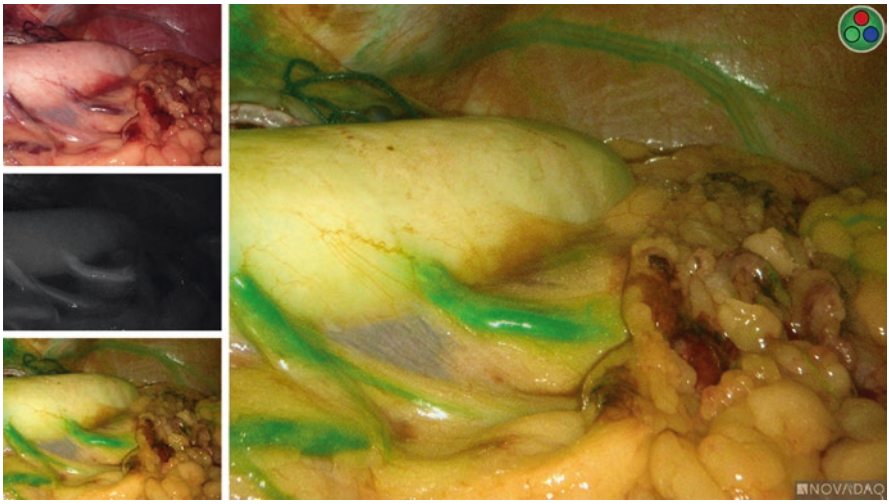

Fig. 12.3 Laser-induced fluorescence of indocyanine green tissue angiography for evaluation of the gastric conduit during MIE

technique, with surgeon experience likely being the most important determinant at present [60, 71–79].

12.6.2.9 Visualization of the Perfusion

Healing of the anastomosis mainly depends on perfusion of the gastric tube. Therefore, identification of a well-perfused part of the stomach for positioning the anastomosis is desirable. Imaging of the tube's perfusion with indocyanine fluorescein seems promising (Fig. 12.3). However, absolute quantification of blood flow is not possible [80–85]. Further studies are needed.

12.6.2.10 Neuromonitoring

Recurrent laryngeal nerve monitoring (RNM) in esophagectomy has been performed for the first time in 2001 by Hemmerling et al. [86]. It took several years until its clinical usefulness has been proven either in the mediastinum or in the neck. It has no impact in operative time, but significantly reduces postoperative vocal cord palsy and consequently pulmonary complications [87–94].

12.6.2.11 Robotic-Assisted Minimally Invasive Esophagectomy

In esophageal resections, surgeons hope to overcome the shortcomings of conventional thoracoscopy with non-articulated instruments due to the fulcrum effect of the thoracic wall, the remote position of the diaphragmatic hiatus and the meticulous lymph node dissection in the upper mediastinum, sparing the recurrent laryngeal nerve and the vagus nerve. Robotic-assisted minimally invasive esophagectomy (RAMIE) promise better maneuverability, motion scaling, tremor filter, and particularly a much more comfortable working position for the

surgeon leading to a smoother workflow with hopefully better outcomes. However, it might be difficult to prove a better clinical outcome for the patient compared to conventional MIE. If a better accessibility to difficult areas in esophagectomy, such as the suprahiatal region as well as the lymphadenectomy in the upper mediastinum, translates into better survival has not been proven yet. Maybe the ergonomic superiority for the surgeon will be the most important aspect in robotic esophageal surgery [39].

12.6.2.12 Lateral Decubitus Versus Prone

Patient positioning for MIE or RAMIE is also under debate: lateral decubitus versus prone position is debated against each other [95, 96].

Prone position of the patient allows for easier dissection of the esophagus since gravity keeps lung and blood down, thereby enlarging the operative field. Therefore, single lung ventilation is not necessary, thus reducing venous shunting. Moreover, it is more ergonomic for the surgeon. On the other hand, lateral decubitus positioning of the patient makes it easier to reach the upper mediastinum in order to perform lymphadenectomy along the vagus nerve. For those coming from open surgery, it offers a similar anatomic aspect and is also better suitable for an emergency conversion to open surgery. To overcome the shortcomings of both methods, a semi-prone positioning with turning the table to the surgeon's needs seems to be a well-accepted compromise.

12.6.2.13 Role of Pyloroplasty or Pyloromyotomy

In a recent systematic review from the UK, pyloric drainage procedure showed a nonsignificant trend towards fewer anastomotic leaks, pulmonary complications, and reduced gastric stasis. However, the ideal technique (botulinum toxin, finger fracture, pyloroplasty, and pyloromyotomy) is still a matter of discussion [97]. During MIE pyloric drainage may increase morbidity in the long term and therefore may be avoided [98]. Nevertheless, in symptomatic patients, an endoscopic pneumatic balloon dilatation (2–3 cm, e.g., with an achalasia balloon) with low threshold can be done at any time postoperatively with low morbidity [99, 100].

12.6.2.14 3D Visualization

For better visual depth perception, 3D cameras seem promising and might even be a more viable technique over 2D in terms of short-term outcomes for patients with esophageal cancer [101, 102]. In the current operation robots, they are standard anyway.

12.6.3 Management of Postoperative Residual Disease

There are no randomized trials exploring the benefit of adjuvant chemotherapy in patients with esophageal or EGJ adenocarcinoma. The management of patients with residual primary tumor or extensive nodal disease after preoperative therapy remains uncertain. Consensus-based guidelines from the National Comprehensive

Cancer Network (NCCN) suggest postoperative chemoradiotherapy [13]. However, management must be individualized based upon clinical circumstances. Administering additional postoperative cycles of chemotherapy has proven difficult due to therapy intolerance. Postoperative radiotherapy ought to be reserved to patients with a postoperatively positive resection margin or bulky disease.

For patients with completely resected pT2N1-2, pT3, or T4 adenocarcinoma, who have not received neoadjuvant therapy, postoperative adjuvant therapy is recommended [103–105].

12.7 Quality of Life, Morbidity and Mortality

The overall incidence of postoperative complications varies widely between 20 and 80% and includes systemic complications (e.g., pneumonia, myocardial infarction) and complications specific to the surgical procedure (e.g., tube necrosis, anastomotic leaks, recurrent laryngeal nerve injury) [60, 106–108]. Pulmonary complications are the most common postoperative complications, occurring in 16–67% of patients [60, 109, 110], but anastomotic leakage occurring in up to 40% of patients has the highest impact on mortality (e.g., 8.9% of in-hospital deaths [49]) [60, 71, 110, 111]. A multivariate analysis identified several preoperative factors that increased the risk of complications following esophageal resection and reconstruction [112]. Some of these included increasing age, conditions associated with compromised pulmonary function (e.g., chronic obstructive pulmonary disease), malnutrition, renal or hepatic dysfunction, and emergency surgery.

Other clinical factors that increase the risk of perioperative (30-day) death following esophageal resection included ascites, increasing age, insulin-dependent diabetes, decreased functional status, renal dysfunction, excess alcohol use, and hepatic dysfunction [71]. However, neoadjuvant chemotherapy or neoadjuvant chemoradiation therapy did not increase the risk of postoperative complications or 30-day mortality [113, 114].

As a conclusion, the high morbidity and mortality of esophageal resections compared to other types of cancer surgery accentuate the need for attempting to lower morbidity in any way such as with the enhanced recovery after surgery (ERAS) concept (see below).

12.7.1 Enhanced Recovery (ERAS)/Fast Track Protocols

Recently, ERAS protocols also found their way into clinical practice enabling an improvement of the results and even lowering overall costs for esophagectomy [115–127].

The current ERAS guidelines for esophagectomy cover all the critically important standard issues associated with enhanced recovery and also address issues unique to esophageal resection (Table 12.3).

Table 12.3 List of society recommendations for enhanced recovery after esophageal resection [10]

Procedure-specific components
• Preoperative nutritional assessment and treatment
• Multidisciplinary tumor board decisions
• Prehabilitation programs; e.g., physical training, preoperative breathing therapy
Operative components
• Timing of surgery following neoadjuvant therapy: 3–6 weeks following completion of chemotherapy and 6–12 weeks following completion of RCTX
• Minimally invasive access whenever possible
• Avoid pyloroplasty (low recommendation)
• Avoid perianastomotic drain
• Restrictive use of NG tube/gastric decompression
• Reduction of number and early removal of chest drains
• Routine use of enteric feeding tubes
• Restrictive perioperative fluid management
• Anesthetic management with early extubation
Post- and perioperative issues
• Restrictive intensive care unit utilization; PCU/HDU as safe alternative
• Perioperative pain control for esophagectomy: peridural, local, avoiding opioids, and early per oral
• Postoperative early nutrition: jejunostomy followed by early oral
• Early mobilization
• Restricted time of central lines, early oral medication
Non-procedure specific
• Preoperative counseling patient/family
• Smoking and alcohol cessation at least 4 weeks before surgery
• Detailed cardiopulmonary assessment
• No bowel preparation
• No preoperative fasting: 6 h for solids, 2 h for liquids
• Postoperative prolonged antithrombotic prophylaxis for 4 weeks
• Avoiding hypothermia
• Postoperative glycemic control below 180 mg/dL serum glucose
• Early bowel stimulation by oral feeding, mild laxatives (Mg)
• Early removal of Foley catheter

12.7.1.1 Prehabilitation Programs

A key determinant of ERAS program success is the rapid return to an acceptable level of functional activity after a major procedure. The process before, termed "prehabilitation," includes a multimodal approach incorporating nutritional intervention (e.g., protein supplementation), medical optimization (e.g., glycemic control, blood pressure control, smoking cessation, alcohol reduction), and psychological intervention (e.g., emotional stress reduction), in addition to a structured and goal-directed exercise program composed of both aerobic and strengthening activity. A long enough interval between neoadjuvant therapy and surgery may contribute to this goal [10].

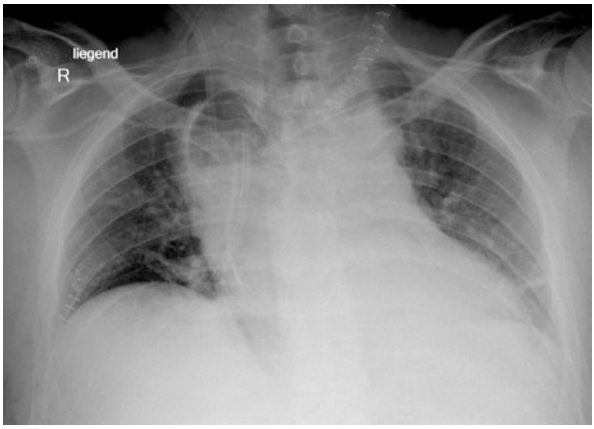

Fig. 12.4 Gastric tube, overinflated by CPAP mask breathing therapy without NG tube decompression

12.7.1.2 NG Tube/Gastric Decompression

Nasogastric tube decompression at the time of esophageal resection is currently recommended with the caveat of considering early removal (on postoperative day 2) when clinically appropriate. Continuous positive airway pressure (CPAP) with high positive end-expiratory pressure (PEEP) can result in bloating the gastric conduit thus producing tension to the anastomosis (Fig. 12.4) [128].

12.7.1.3 Routine Use of Enteric Feeding Tubes

Early enteral feeding with respect to the metabolic rate on day 3–6 should be strongly considered after esophagectomy; either feeding jejunostomy or nasojejunal/nasoduodenal tubes may be used. Enteral nutrition is associated with reduced postoperative complications rates and length of hospital stay in comparison with parenteral nutrition [129, 130]. Early oral feeding has been shown to have positive outcomes in patients who have undergone gastrointestinal surgery. However, there is an increased risk of vomiting and aspiration pneumonia [129]. Oral feeding in the presence of serious complications might not be possible and/or be associated with morbidity and mortality. On the other hand, surgical placement of a feeding jejunostomy was associated with a mortality of 0–0.5% and re-operation rate of 0–2.9%. Other complications noted were entry site infection (0.4–16%), entry site leakage (1.4–25%), and gastrointestinal tract complaints (10–39%) [131].

The ideal route of administration of enteral nutrition in the early postoperative period remains unclear. No recommendation can be given at this time [10].

12.7.1.4 Perioperative Pain Control for Esophagectomy

The choice of analgesia will depend on the surgical approach, the position and size of incisions, and patient factors. The rationale of the ERAS approach is to use multimodal analgesia combined with regional and local anesthetic techniques to allow a patient's opiate consumption to be minimized. This avoids the unwanted side effects of sedation, nausea and vomiting, delirium, and gut dysfunction.

Thoracic epidural analgesia should be considered as first-line approach to postoperative analgesia following esophagectomy [10].

12.7.1.5 Early Mobilization

Despite the postoperative restrictions imposed by pain and various medical devices (e.g., drains, feeding apparatus and pumps), early mobilization should be encouraged as soon as possible using a standardized and structured approach with daily targets to meet [10].

12.7.1.6 Antithrombotic Prophylaxis

Antithrombotic prophylaxis with low-molecular-weight heparin (LMWH) together with mechanical measures and early mobilization, significantly reduce the risk of deep venous thrombosis (VTE). Treatment should be started 2–12 h before the operation and should continue for 4 weeks after the operation. Epidural catheters should be placed no sooner than 12 h from the last LMWH dose. LMWH should not be given until at least 4 h have passed after epidural catheter removal [10].

12.8 Surveillance

No follow-up strategy has ever improved survival or quality of life through earlier detection of recurrent disease. Therefore, on follow-up, focus should be given on clinical signs and history of the patients for indications to CT scan and endoscopy [132–134].

Performing esophagectomy either open or minimally invasive is a very complex surgery. Anatomical and pathophysiological conditions of the abdomen, thorax, and neck have to be considered. Therefore, the surgeon should be experienced in the field of visceral, thorax, and neck surgery, and a high institutional case load (>12/a) is considered a prerequisite for good results [135–137].

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Palliation of Esophageal Adenocarcinoma

13

Etienne Wenzl

Abbreviations

5-FU	5-Fluorouracil
BSC	Best supportive care
BT	Brachytherapy
CRT	Chemo radiation therapy
CT	Chemotherapy
(D)CF	(Docetaxel,) cisplatin, fluorouracil
EBRT	External beam radiation therapy
ECF	Epirubicin, cisplatin, fluorouracil
ECX	Epirubicin, cisplatin, capecitabine
EOF	Epirubicin, oxaliplatin, fluorouracil
EOX	Epirubicin, oxaliplatin, capecitabine
GEJ	Gastro-esophageal junction
FLOT	Fluorouracil, leucovorin, oxaliplatin, docetaxel
G-CSF	Granulocyte colony-stimulating factor
HER2	Human epidermal growth factor receptor 2
HRQoL	Health-Related Quality of Life
MET	Mesenchymal epithelial transition factor
MOS	Median overall survival
ORR	Overall response rate
PDT	Photodynamic Therapy
PEG	Percutaneous endoscopic gastrostomy
PFS	Progressive free survival
PPI	Proton Pump Inhibitor

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_13

PS	Performance Status
RR	Risk rate
SEMS	Self-expanding metal stent
SEPS	Self-expanding plastic stent
TT	Targeted therapy
TTP	Time to progression
VEGFR-2	Vascular endothelial growth factor receptor 2

Adenocarcinoma of the esophagus and gastro-esophageal junction is a highly aggressive and deadly disease. In Western countries, the incidence is rising and has already surpassed the numbers of squamous cell carcinoma in some areas [1]. In a population-based study less than 50% of patients were eligible for surgical treatment (42% received esophageal resection) [2]. Therefore, more than 50% of patients are in palliative setting. This number increases over time, since patients with recurrent disease or incomplete resection most likely will enter palliative treatment with developing efficacy. The group of patients not qualifying for curative surgical resection comprises of those with locally advanced unresectable tumors (T4 invading neighboring organs, predominantly trachea, heart, vessels), distant metastatic disease, carcinosis, and individuals, who deny surgery or suffer on severe comorbidities. The most frequent problem, we have to deal with, is dysphagia (Table 13.1), which finally can lead to complete disability to swallow, malnutrition, loss of body weight, aspiration, and of course to a massive reduction of quality of life. Weight loss of more than 10% worsens the prognosis, in particular this concerns advanced cases. Other tumor-related complications are pain, bleeding, and fistulation, either to the tracheobronchial tree and/or mediastinum (Figs. 13.1 and 13.2). A variety of therapeutic approaches are used, especially to alleviate dysphagia [4], but there is no single "best treatment option" existing, so therapeutic alternatives have to be discussed with the patient and adapted to his/her needs as well to PS. In a survey with 55 gastric and GEJ cancer patients, under palliative CT ability of self-care and tolerability of therapy were rated highest in importance [5]. So patients' view is not necessarily in congruence with specialists' opinion. Palliative therapy needs a multimodal and multidisciplinary approach and should be reviewed in an oncological tumor conference.

Table 13.1 Dysphagia score (Mellow and Pinkas [3]) to assess therapeutic efficacy

0 = able to eat normal diet/no dysphagia
1 = able to swallow some solid foods
2 = able to swallow only semi-solid foods
3 = able to swallow liquids only
4 = unable to swallow anything/total dysphagia

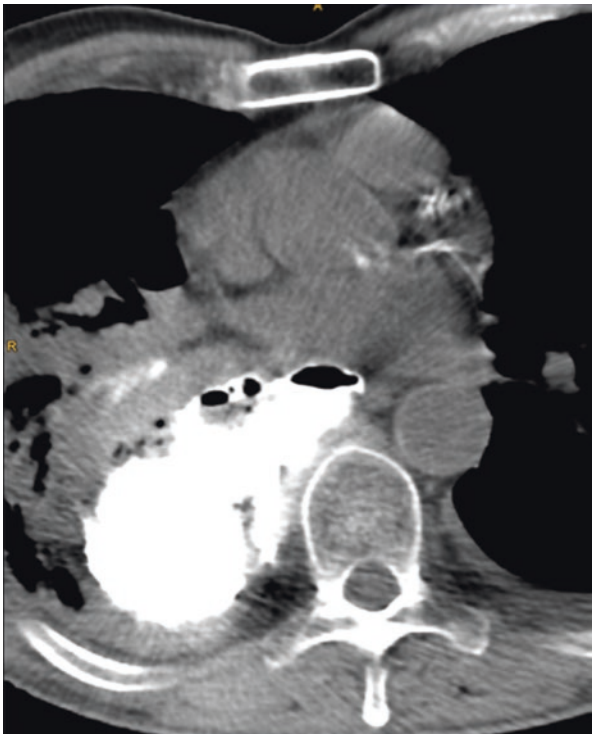

Fig. 13.1 CT scan of a patient with esophageal cancer, showing the spacious and devastating distribution of the contrast media within the mediastinum caused by a tracheo-esophageal/mediastinal fistulation

Extracting data and further more drawing conclusions for options of palliative treatment have to be done very carefully. This is mainly due to different design of the studies. Prognosis in patients on palliative track seems mainly dependent on possibilities to apply antitumor therapy [6]. Knowledge of prognostic factors (e.g., weight loss, PS, ability to swallow, pain) will help to determine the right choice of therapy [7]. Clinical outcome and patient-related outcome are not necessarily linked together. Surprisingly, as example, DCF compared to CF gives better results of HRQoL, although DCF is accompanied by higher toxicity [8]. One possible explanation for this unexpected finding is that more aggressive therapy might increase patient's hope and tolerance.

13.1 Palliative Chemotherapy

Adenocarcinoma of the esophagus and GEJ is assumed to have a very similar profile as gastric cancer [9] and therefore frequently dealt together. Restrictively it must be admitted that differences seem to exist [10].

There is consensus that a CT should be offered to patients with incurable tumors and physical fitness [11]. The goal is to extend survival time [10], improve/maintain HRQoL, and restore/maintain organ function. This benefit is questioned for

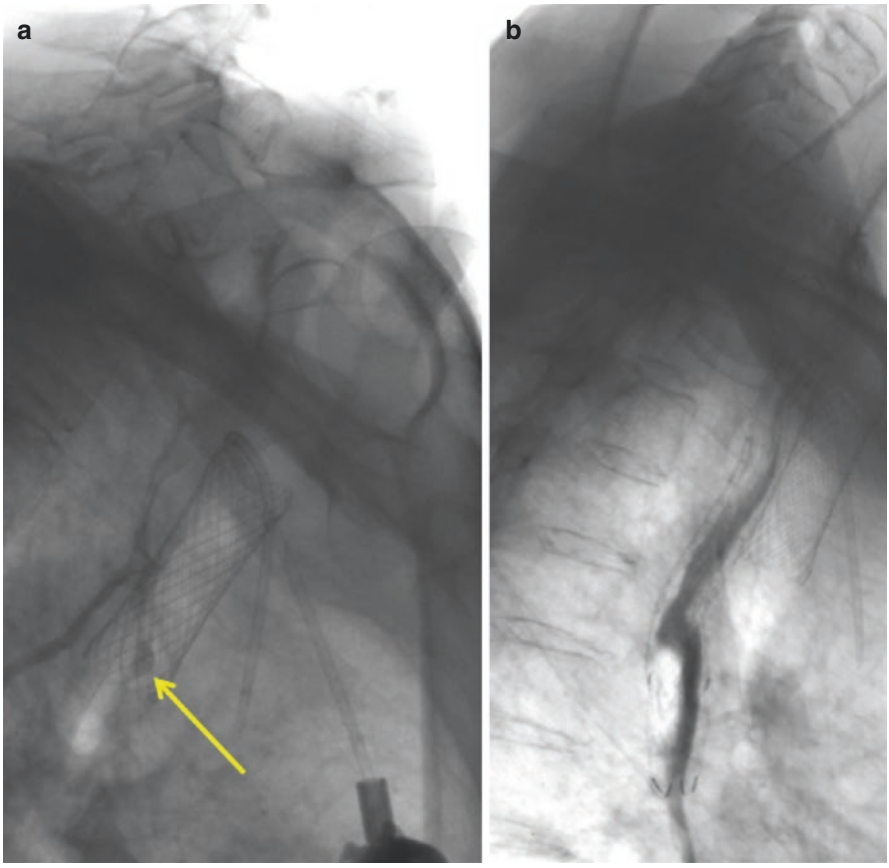

Fig. 13.2 Effect of stenting on a tracheoesophageal fistula. (**a**) Depicts a residual leakage (arrow) after a tracheal stent (Leufen aerstent® TBS, fully covered, 16/40 mm) was placed. (**b**) An additional esophageal stent (Niti-S™ Esophageal Stent, fully covered, 18/100 mm) was implanted, which led to a separation of the esophageal and tracheal compartment, preventing aspiration

individuals with reduced PS. There is some ongoing debate, whether CT is able to improve or just slow down deterioration of HRQoL [12]. It is still a controversy, which combination and substances should be applied, and also guidelines with slightly different recommendations exist. Most used chemotherapeutic regimens are based on combination of cisplatin and 5-FU. A randomized study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin confirmed noninferiority. PFS and RR were comparable, and median survival was ECF: 9.9 months, ECX: 9.9 months, EOF: 9.3 months, and EOX: 11.2 months with a HR for death of 0.8 for EOX over ECF. Toxicity was similar for fluorouracil and capecitabine, whereas oxaliplatin caused more neuropathy and less renal toxicity [13]. If a standard of care is combination of platins and fluoropyrimidines, expanding this to a

triplet with docetaxel achieves better results (DCF vs. CF, ORR: 37% vs. 25%; median TTP 5.6 vs. 3.7 months; MOS: 9.2 vs. 8.6 months) [14, 15], although having to pay the toll of higher hematologic toxicity (Neutropenia Grade 3–4: 82% vs. 57%). DCF-treated patients also had better HRQoL [16] and clinical benefit in terms of maintaining PS and body weight. There was no measurable impact on pain or opioid need [17].

Various modifications have been developed, searching for better tolerability than the DCF regimen, e.g., FLOT [18] or adding G-CSF [19]. Since capecitabine was found to be equal to 5-FU [13], most patients, if possible, prefer oral administration and furthermore implantation of a venous access device can be avoided or at least delayed. A meta-analysis including almost 3500 patients, searching for optimal first-line CT demonstrated an advantage of triplet over doublet CT (OS: HR 0.90; PFS: HR 0.80; objective response rate risk ratio: 1:25). In contrast, risk of thrombocytopenia, mucositis, and infection increased [16]. No statistical significance was found with adding anthracycline to a doublet. This contrasts with Wagner's publications [20, 21], whereas all other results mainly conform.

After failure of first-line therapy, the COUGAR-02 trial proved the efficacy of second-line monotherapy with docetaxel versus BSC. MOS was found 5.2 versus 3.6 months as well as reduced dysphagia and pain [22]. In a comparison between irinotecan and paclitaxel, no relevant differences were detected, so both can be applied as second-line therapy [23]. Reliable data to second-line CT are still scarce and it remains an individual therapeutic decision depending on patient's preference and PS [24].

In a recently published Cochrane review, it has been shown with high quality of evidence that in palliative setting CT and/or TT increase OS (MOS: 6.7 vs. 5.7 months, HR 0.75), furthermore adding only TT improved also PFS (HR 0.64, moderate quality of evidence). These therapies seem to increase toxicity grade ≥3, whereas there was no clear proof for increased treatment-related mortality. Only very low evidence was found in a small sample for the improvement of HRQoL [10].

13.2 Targeted Therapy

The ToGA [25] trial investigated the efficacy of adding trastuzumab to a CT, targeting human epidermal growth factor receptor 2. It showed an increased MOS of 13.8 over 11.1 months in HER2 positive tumors. So, a HER2 status should be determined for selecting cases, which will benefit from adding trastuzumab. Trastuzumab should not be administered with anthracycline simultaneously.

A further promising antibody is ramucirumab, which acts against VEGFR2, blocking angiogenesis. A significant better survival was shown in the REGARD [26] trial (Ramucirumab vs. BSC, 5.2 vs. 3.8 months) and RAINBOW [27] study (paclitaxel plus ramucirumab vs. paclitaxel monotherapy, 9.6 vs. 7.4 months). Ramucirumab was also proven to increase OS and PFS in patients previously treated with chemotherapeutic agents [10]. Other tested monoclonal antibodies and tyrosinkinase inhibitors did not show high antitumor effects, and a study directed

against hepatocyte growth factor receptor (MET) was interrupted due to high mortality in the treatment group [28, 29].

Taken together, application of targeted therapies increases MOS and even PFS in palliative setting. It is still somehow open, from which patient profile benefits the most.

13.3 Palliative Radiotherapy and Chemoradiotherapy

Radiotherapy definitely plays a role in the therapeutic spectrum of esophageal cancer. It is a valid alternative/addition for palliation. There is a reasonable effect reported on symptom control, particularly dysphagia. This can be accomplished by EBRT or BT and also by combination of both or other measures of recanalization of the esophagus. New techniques in planning and delivery of radiation are expected to allow higher precision in targeting the tumor and therefore reducing damage to surrounding healthy tissue [30]. Probably RT, stent placement, or a combined management of both are mostly applied. Two randomized studies [31, 32] compared BT with stent placement, and the bottom line was that initially stents are more effective, whereas the esophageal patency of BT lasts longer [33], latter is in line with HRQoL [34]. Complications were less in the BT group (21% vs. 33% [31] or 13% vs. 25% [34]). Stenting appears very appropriate in patients probably expecting short survival. In a further randomized trial, increasing evidence emerges supporting the combination of SEMS and BT [35] as a very efficient method. Adding EBRT (30 Gy/10 fractions) to high-dose-rate BT (8 Gy/2 fractions 1 week) proved superiority to BT alone in a randomized study. This affects dysphagia, odynophagia, regurgitation, pain, PS, and HRQoL, whereas MOS and severe adverse events did not differ [36, 37]. The efficacy and safety of BT are reviewed in a recent meta-analysis [38] with resolution of symptoms in 87% after one month, a low mortality rate of 0.3%, and adverse effects of 23.4%. A more frequent use of BT is advocated, but it must be admitted that availability of BT is not everywhere.

A comparison between CRT (50 Gy) and RT alone (64 Gy) clearly demonstrated an advantage in favor of CRT (MOS 14.1 vs. 6.3 months) [39]. These results also get supported by a retrospective study comparing survival of SEMS versus CT versus RT versus CRT with MOS of 6.92, 7.75, 8.56, and 13.53, respectively. The only independent predictor in the multivariate analysis was the treatment modality [40]. Similar supporting results were obtained by a review primarily focusing on patient-related outcome [8].

13.4 Stenting

Introduction and continuous further development of expandable stents have brought a big advancement in treating dysphagia. Easy handling during placement, better results, and less complications led to a nearly complete replacement of the older plastic tubes. Such tubes were associated with high clinical mortality (>10%) and

complication rate [41, 42]. There are many expandable stent models offered, made either of an alloy of nickel and titan or steel or plastic (SEPS). The use of SEPS is highly decreased because of a higher migration rate and therefore need of further interventions. At the time being, SEMS are mostly used, fully or partially covered with synthetic covering—to prevent tumor ingrowth, with or without a reflux valve. Double-layered (second external metal mesh around a covered stent) is expected to reduce migration. Alternatively, biodegradable models are available, which in first-line seem more appropriate for benign diseases. To discuss different brands of stents goes beyond the scope of this chapter due to different availability, variety and rapid change in design and technical aspects. Selection of the most appropriate stent has to be done depending on the tumor location, size, configuration, and length of stenosis [43]. Placement is performed endoscopically or radiologically in sedoanalgesia or in general anesthesia, in selected cases with expected difficult stent placement or high risk of aspiration. Typical complications in the early phase are perforation, aspiration, pneumonia, pain, migration, and reflux. Late complications are migration, recurrent dysphagia due to tumor in- and overgrowth, food impaction, bleeding, formation of an esophageal fistulation, particularly to the airways, migration, perforation, and reflux. Stents placed over the GEJ form an open channel allowing reflux of gastric juice. To overcome this problem, stents with integrated reflux valves were introduced. The value of these is not clearly defined [44] and has to be compared with PPI administration. Although stents provide a rather rapid relief of dysphagia, the disadvantage is recurrent dysphagia within a few weeks. So, it appears reasonable to combine stent with BT notably for patients with estimated longer life span [31]. Feasibility and safety of this additive treatment have been shown, although a substantial increase of HRQoL except relieving dysphagia was not observed [45, 46]. Further promising results are expected with SEMS covered with ^{125}I seeds providing prolonged survival compared to covered SEMS (MOS 177 days vs. 147 days) with comparable side effects [47].

13.5 Other Palliative Treatment for Alleviation of Dysphagia

Different further measures are used to achieve relief from dysphagia. Thermal and chemical methods are locally applied like laser, photodynamic therapy, argon plasma coagulation, and injection of ethanol. Probably APC is the most used thermoablative method, which seems technically easier to apply with a reduced risk of perforation compared to laser [48]. In a randomized comparison of APC alone to a combination with either BT or PDT, a longer dysphagia-free period was observed for combined modalities, whereas these did not differ from each other. As well less complication as better HRQoL was shown in the APC-BT group [49]. In addition, availability of laser and PDT is limited and also requires specialized experience. Photosensitization of the skin and a distinct danger of perforation as side effects of PDT also must be taken into account [50].

In a meta-analysis, comparing the outcome between SEMS and other locoregional palliative treatment methods, stents needed less recurrent interventions,

whereas a survival advantage was observed for the others [44]. So, recanalization with other methods apart from SEMS are mainly used, if stents cannot be placed, e.g., in situation where the tumor is very close to the upper esophageal sphincter.

Mechanical dilation can be applied as an adjunct to widen the esophageal lumen before inserting a stent. The sole use of dilation is only recommended for selected cases with poor prognosis.

13.6 Role of Surgery

Besides attempts of rescue surgery, mainly due to perforation or bleeding, nearly all of palliative surgery and bypasses became obsolete because of high rates of morbidity (30–70%) and mortality (20–40% in the literature) [51–53]. This in turn leads to prolonged hospital stay and reduced HRQoL.

Nevertheless, some reports advocate palliative resection. Independent prognostic variables, which lead to poor survival, were identified as local or diffuse peritoneal carcinosis, solid organ matastases, signet cell histology, ASA III–IV, and advanced tumor stage [54]. This management applies only for a very small and highly selected group of patients. And it has to be noted that this study mainly focuses on OS but not on HRQoL.

One has also to bear in mind that development of new drugs, targeted therapies, and radiation techniques might offer new therapeutic approaches [55]. So, the border of unresectability might shift towards potential radical resectability due to downsizing and/or downstaging of the tumor. This could affect locally advanced tumors as well as metastatic ones in selected cases. The role of ablative therapy of metastases needs still to be defined.

13.7 General Supportive Measures

Pain medication, psychooncological support, and if required social help must be offered to patients with esophageal cancer. This should help these individuals to alleviate problems induced by this heavily aggressive disease. Nutritional status plays a major role and it has been shown that it is predictive for the course of the disease [56]. In some cases, a PEG tube is required, where oral intake cannot be achieved with other measures. This mainly applies for tumors highly located.

13.8 Conclusion

Palliative therapy of esophageal cancer has to be adapted to PS, concomitant diseases, organ function, morphology, and complications of the tumor. It should minimize the requirement for multiple therapeutic sessions and of course be in concordance to needs and wishes of the patient. This therapy is based on the concept

of multimodality and multidisciplinarity. If PS is good, a systemic CT and/or TT should be offered. This increases OS and has some positive effect on PFS and HRQoL. If first-line CT fails, a second-line CT and/or TT should be pursued. Oral food intake needs also to be restored. In case of reduced PS patency of the esophageal canal (e.g., stent/BT) and BSC are the foremost aim of palliation, providing the highest possible level of HRQoL. In some selected cases, a reduced systemic therapy might be appropriate.

13.9 Final Remark

This chapter was also crosschecked with selected published guidelines [11, 57–61].

Acknowledgments I grateful thank M. Cejna for providing the radiological images and discussing the manuscript.

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14 Multidisciplinary Management: Alternative Perspectives for the Management of Gastroesophageal Reflux Disease (GERD) and Barrett's Esophagus (BE)

Martin Riegler and Sebastian F. Schoppmann

14.1 Introduction

Symptomatic gastroesophageal reflux disease (GERD) affects 20–30% of the population, and thus represents one of the most frequent disorders of the upper gastrointestinal tract [1–3]. Factors associated with GERD include heredity, age, and lifestyle (nutrition, obesity, eating disorders, drug consumption) [1–3]. GERD affects the life quality and the well-being due to the symptoms (heartburn, wheezing, cough, asthma) and the morphological consequences including an increased cancer risk for those with Barrett's esophagus (BE) [4–7]. Economically, GERD matters as a frequent reason for sick leave [7]. In addition, diagnosis and therapy of GERD and BE foster the development of novel technologies [1, 2, 4, 5, 7]. This continues to entertain new promising niches for the industry and health-related economies. Furthermore, diagnosis and therapy of GERD and BE cause economic burdens for private and public health security systems [1, 7].

Due to the anatomical associations of the esophagus, reflux can affect the esophagus, ear, nose, throat (ENT), mouth, tongue, teeth, and the lungs. Therefore, GERD and BE management requires a *multi-* and *interdisciplinary* approach [1, 3, 7]. Accordingly, this book aims to summarize a novel understanding regarding the diagnosis, therapy, and follow up of patients with GERD and BE. The incidence and frequency of asymptomatic reflux without and with BE are not known. Individuals without symptoms do not seek medical care. However, the majority of those developing esophageal cancer lack a GERD symptom positive medical history. Here we

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_14

aim to elucidate the current difficulties related to the diagnosis and therapy of GERD and BE, and how they could be overcome. Special attention addresses the question, in as much the translation and application of ancient wisdom contribute to improve GERD and BE management [8–11].

Our scientific journey follows the idea that histopathology represents a sensitive diagnostic marker for reflux, GERD, and BE management (diagnosis, therapy monitoring, follow up) [12–21]. In contrast to symptomatology, endoscopy, and function test data, histopathology assesses reflux at the cellular level (increases resolution) [12–21]. According to this concept, the presence of columnar-lined esophagus (CLE) with and without cancer risk (BE) serves as a marker for reflux (no CLE without reflux) [14–21]. Reflux is considered a disease in the presence of life quality impairing symptoms and cancer risk. As such cancer risk (BE) ± symptoms or symptoms with cancer risk (BE) negative CLE defines *disease*. Columnar-lined esophagus (CLE) without cancer risk (BE) and symptoms defines *abnormality*. Absence of any CLE defines normalcy. Disease requires therapy (lifestyle, medical, interventional). The finding of abnormality and normalcy translates into strategies for disease prevention (lifestyle measures).

14.2 Symptoms and Signs

Conceptually, disease management should focus on the cause. Since many years, GERD management is based on a complex mixture of symptoms, endoscopic information, histopathological findings, measures obtained during esophageal function test (manometry, reflux pH-monitoring), and radiological examinations [22–28]. As a consequence GERD has been described, categorized, and assessed, using terms, which fostered the impression of a complicated and confusing babylonian linguistic confusion. While the moon shades light on changes, the beautiful spectrum of classifications tours from Montreal to Rome, from Vienna to Los Angeles, from Chicago to Prague, and from there to Milan [22–28]. Through the internet, physicians and patients learned about nonerosive reflux disease (NERD), erosive reflux disease (ERD), gastroesophageal reflux disease (GERD), functional heartburn (HB), hypersensitive esophagus, normal Z-line, irregular Z-line, small and large hernias, tongues, island and segments of columnar-lined esophagus (CLE), endoscopic Barrett's esophagus, confirmed Barrett's esophagus, ultra-short Barrett's esophagus; definitions for normal and abnormal manometry and reflux monitoring [2, 7, 21, 26]. The problem was that we were not allowed to know: what is normal? What defines normalcy? Is it the absence of any reflux? Is it the absence of any symptoms? Is it the absence of any CLE? Does the presence of CLE, BE without symptoms define a disease or an abnormal condition? Does it need the presence of symptom negative, but low- or high-grade dysplasia positive CLE to be recognized as a disease? Which measures define normal, physiologic reflux? How many symptoms per week, per month, per year define normalcy? How often do you have to

perceive symptoms to be categorized as abnormal, as having a disease? What means the term "troublesome"? What defines a symptom to be categorized as "troublesome"? Which measures, numbers and values define the landmark, and the cutting edge between normal and abnormal and between physiologic and pathologic? At which point do GERD and CLE start to become a disease? Why did we get into trouble at all? What are the reasons for the above insecurities? It seems that our current conduct of reasoning hides ourselves from a suitable and reliable marker for the definition of GERD. It seems that our current approach towards GERD and BE prevents us from recognizing the most valuable and reproducible indicator for reflux, GERD, and BE.

14.3 GERD and Cellular Pathology

Going in line with Carl von Rokitansky (1804–1878) and Rudolf Ludwig Karl Virchow (1821–1902), *cellular* pathology and histopathology define a disease [21, 29, 30]. As such histopathology defines diseases of the liver, pancreas, kidneys, lungs, thyroids, adrenals, colon, intestine, prostate, bone, muscle, skin, nerves, and brain. Would there be the possibility for a histopathological definition of GERD? Does it need the development of low- and high-grade dysplasia and cancer to get recognized as a disease in those without symptoms (heartburn, regurgitation)?

Twenty years ago, the pathologist *Para Chandrasoma* and the surgeon *Tom DeMeester* critically revisited the criteria used for the definition of GERD and did what medicine used to do since the times of Rokitansky and Virchow: to base the diagnosis of a disease on *cellular pathology*, i.e., histopathology [12–16]. Their cautious search correlated the histopathology to the function of the esophagus and aimed to examine the qualities, which contributed to the orchestration of symptoms, signs, and cancer risk [12–16, 31, 32]. And the articles collected within this book nicely demonstrate, what happens, if you allow the use of histopathology for the definition of a disease: you receive an advantage. Going in line with the above statement, that *something* prevents us from recognizing the most valuable marker for GERD, we are led to a very old concept of reasoning. Within this concept, man recognized the world as a spectrum of hidden atmospheres and unhidden perceptions. You cannot see an atmosphere, but *something* you see may evoke a particular atmosphere (astonishment, excitement, happiness, humility). Atmosphere may contribute to focus your attention into a specific direction. Therefore, the legacy of our ancient Greek forefathers contains important relevance for the understanding of GERD and BE. In addition, it motivates to search for a common, underlying cause of any observation, perception, and phenomenon, i.e., GERD, NERD, BE, heartburn [7–11]. Now we are going to explore and investigate the relevance of this approach for a *distinct* understanding of GERD and BE.

14.4 Hesiod Unfolds GERD and BE

Most excitingly, the GERD story contains a lot of similarities that have been expressed within the *Theogony* of the ancient Greek thinker *Hesiod* (around 700 B.C.), where we are *allowed* to read [33]:

> *But hateful Strife bore painful Toil and*
> *Forgetfulness and Famine and tearful Sorrows and*
> *Discord*

This fascinating "fragment," this wonderful poetic biopsy points out the *reason* and the major consequences of a disease (for example, GERD): the cause for painful toil, tearful sorrows, and discord [33]. The list of terms including painful toil, tearful sorrows, and discord describes the ancient version of so-called *somatic* and *psychosomatic symptoms*. Most strikingly, Hesiod understood and explained the reasons for the symptoms: *forgetfulness* and *famine*. Furthermore, forgetfulness and famine originated within "hateful strife." In ancient Greek, forgetfulness (*lethe*) and famine (*limos*) describe the qualities of a very old concept serving the understanding of phenomena [10, 11].

Briefly: forgetfulness, *lethe*, is the famine (*limos*) of memory (lack of memory); as such the *limos*, the deficiency, the hunger, the absence, the lack of something, equals the very cause of all phenomena [10, 11]. *Limos*, the deficiency, the lack of something represents the reason and prerequisite for all things that we can perceive (without the well-oriented and distributed lack of the white background color we could not read the words in this book) [8, 9]. The entire ancient Greek mythology, tragedy and epic poetry (Hesiod, Homer, Sophocles, Euripides, Aeschylus, Pindar, Anaximander, Heraclitus, Parmenides) explains the world as the manifestations of limos (hunger, deficiency, lack of something) and lack of memory (forgetfulness; lethe) [11]. According to the ancient Greek reasoning, *lethe* and *limos* orchestrate the background against which we are allowed to reason, think, and consider perceptions (i.e., esophagitis, Schatzki ring, esophageal cancer) [10, 11].

Lethe describes the hidden (i.e., lack, *limos*, of perception), the things we are not allowed to see, because they are hidden, away from our perception, behind another thing, etc. At this point we arrive at the central aspect of our understanding: if you unhide the *lethe*, you will get *a-letheia*, and this is the term which simply describes the truth! *Aletheia* unhides the term, that all philosophy and thinking is about [11]. The ancient Greek thinkers Anaximander, Heraclitus, and Parmenides contributed their lives to explore the relations between *lethe* and *a-letheia* [11]. As such we understand, how the ancient Greeks, our forefathers, spoke about truth: truth for them was the unhidden, the things they were allowed to perceive, see, assess, measure, and *diagnose*. But they understood, that trouble and insecurity arise from those thing, that we were *not* allowed to see, because they were hidden to us, hidden from our perception: *lethe*. And here we face the essence of the ancient Greek reasoning and mythology (= the collection of ancient knowledge). The interplay between *lethe* and *a-letheia*, the hidden and the perceivable, Shakespeare's, Hamlet's "to be or not

to be," unfolds the tension-rich playground for Greek philosophy, poetry, epic, and architecture [8–11]. Ancient Greece is all about *lethe* and *a-letheia* and therefore about existence and being. And the circuit of reasoning is closed by the understanding that *lethe* represents the deficiency, lack, limos of *a-letheia* [11].

Based on the above considerations, the *essential character* of all perceptions unfolds as a manifestation of *limos*. Since *limos* indicates "deficiency," "lack of something" it seems justified to follow that any perception equals a form of "*lack limos*" [8, 9]. Phenomenologically shadow represents *lack limos* of light, silence represents *lack limos* of sound, secret means *lack limos* of information, absence mirrors *lack limos* of presence, disease equals *lack limos* of health, and *a-letheia* is *lack limos* of *lethe* [8–11]. The latter mirrors the "*cellular pathology"* of our being, existence, and atmosphere. Taken together, the term "lack limos" indicates "deficiency" and/or "the lack of something." If all perceptions (GERD symptoms, diagnostic signs) represent a form of *lack limos*, we have to search for a possibility to *overcome* (theory) and *compensate* (praxis) this state of deficiency.

Fortunately, Hesiod describes a way to unhide the *lack limos* of information and replace it by unhidden knowledge: the *muse*. The term "muse" can be traced back to the levantine cultures (1500 B.C.) and describes the concept of strict order and *discipline* for achieving success. At the beginning of the theogony, Hesiod calls the *muses* to support his project [34]. Now you may ask: what the hell does Hesiod and these terms have in common with GERD? Did Hesiod suffer from GERD? Basically we do not know that, there exists no record regarding the medical history of Hesiod, although it can be assumed that Hesiod had an esophagus (Greek: oiso—carry, transport; phagein—the food; i.e., the transporter of the food) [35], that presumably also has been lined by columnar epithelium, at least to some extent. Thus, it may be justified to assume that Hesiod had at least quiet asymptomatic reflux. We will go back to it later.

The poetry of Hesiod motivates us to take a look at GERD, using a *different* perspective. We may question, in as much GERD translates into a collection (Greek: logos) of "lack limos" forms of deficiencies, of absences, of *limos* and *lethe*. And what about forgetfulness, the absence of memory, the lack of remembrance within the patient history and the medical community [8–11]? May it be that GERD and BE collect a broad spectrum of forms of deficiencies? A collection of forms of *lack limos*? Could it be that Hesiod (700 B.C.) had given a future outlook containing major relevance for our present time (2019 A.D.)? Are we caught back to our roots after a time span of 2719 years?

14.5 GERD as a Collection (Greek: Logos) of Lack *Limos* Deficiencies

During the conduct of the book you saw, that the modern understanding of GERD in fact goes in line with the Hesiod concept of lack *limos* (deficiencies) and *lethe* (the hidden, out of memory, out of perception) [9–11]. As depicted in Table 14.1, GERD represents a "beautiful" collection of *lack limos* (deficiencies) and lethe-type

Table 14.1 Spectrum collection of deficiencies (lack limos) related to gastroesophageal reflux disease (GERD and Barrett's esophagus (BE), as outlined in the text

Type of lack limos deficiency	Consequence	Compensation by
Lack of lower esophageal sphincter function	Sphincter failure and gastroesophageal reflux	Diet, anti-reflux surgery
Lack of esophageal transport function	Sphincter failure and gastroesophageal reflux	Diet, anti-reflux surgery
Lack of resistance against normal, physiologic reflux	Abnormal, increased reflux and acid exposure, positive symptom correlation	Diet, transient proton pump inhibitor therapy, anti-reflux surgery
Lack of adequate lower esophageal and hiatal geometry	Hiatal hernia, lower esophageal sphincter failure	Hiatal hernia repair
Lack of normal tissue	Inflammation, columnar-lined esophagus (CLE), Barrett's esophagus	Transient therapy with proton pump inhibitor; ablation in the presence of cancer risk Lower esophageal sphincter repair
Lack of esophageal patency	Stenosis, dysphagia	Dilatation, stent, surgical repair
Lack of adequate resolution	Limited endoscopic information	Replace endoscopic by cellular pathology, i.e., histopathology, i.e., Chandrasoma classification
Lack of adequate electrical tissue resistance, as assessed by impedance test, lack of tight junction integrity	Leaky squamous epithelium, reflux-induced inflammation, dilated intercellular spaces	Elimination of reflux by diet or anti-reflux surgery
Lack of awareness and knowledge for healthy nutrition	Consumption of food and beverages containing concentrated sugar	Low-carb diet
Lack of adequate awareness for the cause of reflux, GERD, and BE	Symptomatic therapy, instead of cause related therapy	Repair the cause of the disease by diet and/or anti-reflux surgery

phenomena. The reason for GERD is not the gastric acid, not the development of symptoms, stenosis, Barrett's esophagus, and cancer. A modern understanding unhides, that the reason for GERD is the dysfunction of the lower esophageal sphincter: lack of adequate sphincter function, i.e., limos (deficit) of appropriate sphincter function [20, 36–40]. This has already been pointed out by the early papers of Tilestone 1906, Jackson 1929, Allison and Johnstone, and Norman Barrett in the 1940s [41–46]. But it seems that the medical community somehow did forget about it: lethe, forgetfulness, lack of remembrance comes into play.

Then around 1994, Chandrasoma and DeMeester synchronized their interests and started to unhide (a-letheia) and remember the sequence of events leading to GERD: dysfunction of the lower esophageal sphincter fosters reflux, which in turn causes the return of the gastric acid juice into the esophagus. As a consequence, the esophagus inflames and changes its lining, the squamous lining is replaced by a columnar-lined mucosa [47], and the so-called columnar-lined esophagus (CLE)

[12–20]. And if the CLE contains goblet cells, we name it Barrett's esophagus and we speak about Barrett's esophagus [31]. Thus, we refer to the paper published by Norman Barrett in June 1957 in Surgery, where he coined the term columnar-lined esophagus [48].

Going in line with the Hesiod terminology [33], lack, limos, deficiency of adequate function of the lower esophageal sphincter causes reflux, this reflux causes the lack, loss, limos of normal white squamous epithelium, which gets inflamed and replaced by columnar-lined esophagus, i.e., the esophagus loses its normal mucosa, this is lack limos of normalcy (Figs. 14.1 and 14.2). Over time progression of GERD causes lack limos of adequate esophageal and hiatal anatomy and geometry (Fig. 14.2) [16, 19, 49, 50]. In addition, the lack limos of sphincter function causes the symptoms (pain, sorrow) and inflammation, i.e., the discord of the immune system, using the words of Hesiod.

Over time the lack limos of appropriate function of the lower esophageal sphincter induces increased reflux (± acid pockets) which in turn affects the transport function of the esophageal body, resulting in lack limos of adequate esophageal bolus transport function. As such, GERD progresses with all its manifestations including

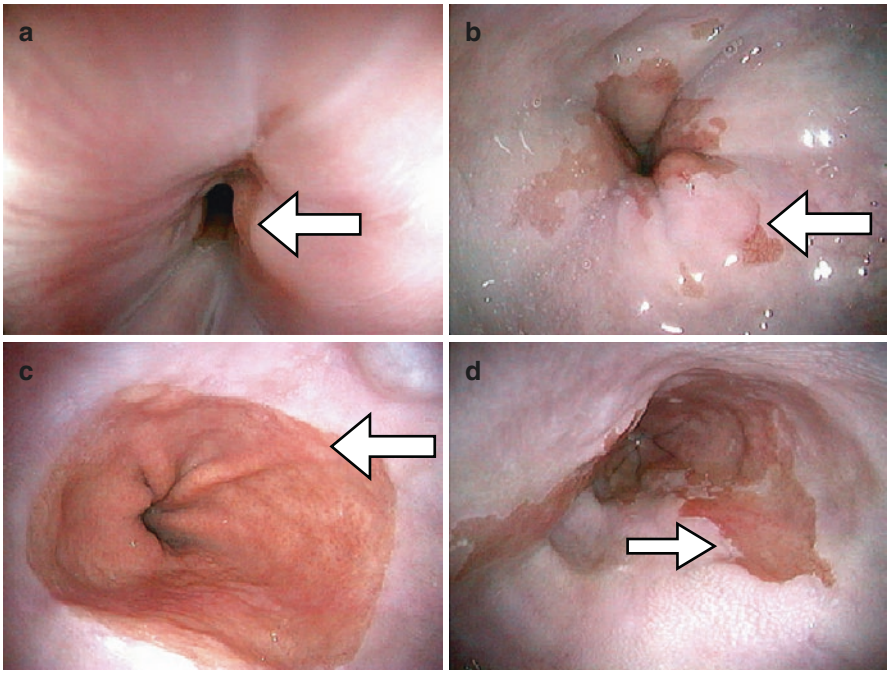

Fig. 14.1 Antegrade endoscopic view into the lower end of the esophagus with the squamocolumnar junction (SCJ) at (arrow in **a**), and *above* the level of the diaphragmatic impression (**b**–**d**). Note the presence of endoscopically visible tongues and islands of columnar-lined esophagus (arrows in panels **b**, **d**) and prominent rugal folds (arrows in panel **c**). The histopathology of SCJ biopsies revealed columnar-lined esophagus (CLE) without (**a**–**c**) and with non-dysplastic Barrett's esophagus (**d**)

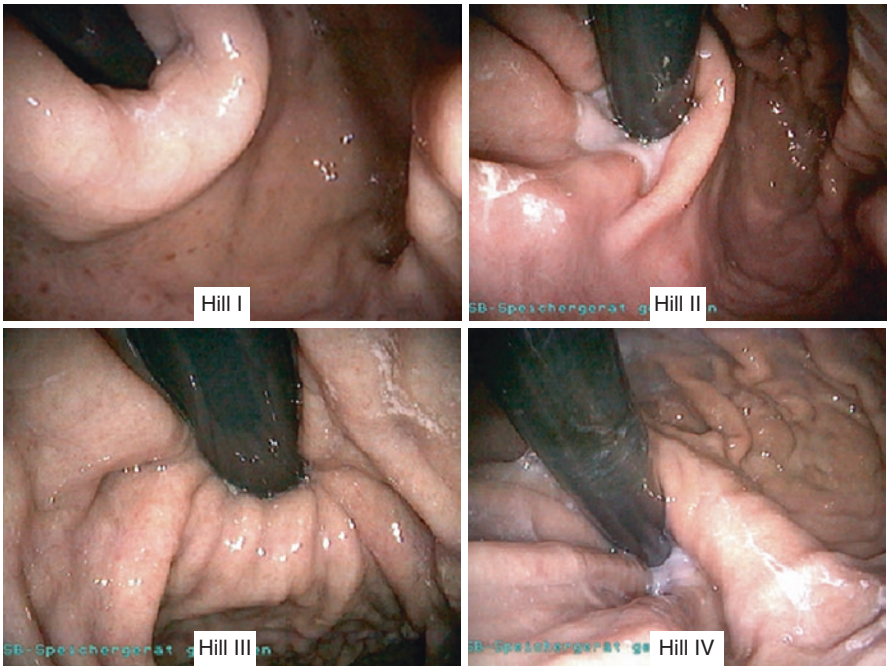

Fig. 14.2 Hill classification of the esophagogastric valve, as obtained during retrograde endoscopy. Note, that with increased Hill grade, the esophagogastric valve loses the capacity to adequately enwrap the endoscope. The *lack limos* of Hill valve integrity mirrors the failure of the lower esophageal sphincter function, geometry, and anchorage within the diaphragm, as described in the text

symptoms, impaired patency, food intolerance, sleeping disorders, anxiety, depression, and cancer. Could we stop the progression of GERD? Is there a perfect point, at which progression of GERD should be stopped? May symptoms help to define that point?

14.6 Lack Limos of Symptoms

As a matter of fact, the large majority of those developing the most severe consequence and complication of GERD, esophageal cancer, appear without a preceding history of symptoms [2, 4–7]. So, symptoms did not work as a reliable marker for GERD in these patients. But how can people without symptoms, without having GERD symptoms, develop a GERD-induced cancer?

Here, morphology (the collection of tissue data) entered the stage: we discovered that Barrett's esophagus is the precursor to cancer and may be assessed by histopathological examination within biopsies obtained from an irregular Z-line, tongue, or island of endoscopically visible columnar-lined esophagus [2, 4–7, 10, 11, 15].

But how should we deal with Barrett's assessed at an endoscopically normal appearing esophago-gastric junction? [18]. Where and how do we define the normal esophago-gastric junction? What about Barrett's within an endoscopically completely normal appearing esophago-gastric junction? What about dysplasia and early cancer within an endoscopically normal appearing esophago-gastric junction? What about the importance of magnification for the discrimination between normal and abnormal findings? For more than 30 years, symptoms and endoscopic criteria defined GERD [22–25]. Histopathology of biopsies obtained from the endoscopically visible squamo-columnar junction (SCJ) came into play, when Barrett's esophagus was assessed [2, 18, 19]. Today we know that we can do much better. Today we see that the information gained at the highest light microscopical magnification resolution is most suitable for the definition of reflux, GERD, cancer risk, therapy monitoring, and follow-up [7, 15, 19–21]. And this intriguing aspect is also well taken by the book.

14.7 Lack Limos of LES Function

The correlation of function test data and histopathology demonstrated that the failure of the function of the lower esophageal sphincter (LES) represents the cause of GERD and BE [31, 32, 36, 51]. Over time, lack limos of LES function contributes to orchestrate symptoms and signs of the disease [7, 16, 27].

Conceptually, LES failure and dysfunction may be mediated by genetically weak formatting of the connective tissue, mechanical stress, which in turn contribute to unfold and open the LES; and drug-induced impairment of LES function. These are the reasons for LES failure:

1. *Hereditary factors:* genetics for the formatting of weak tissue and sphincters (inguinal hernia, connective tissue disorders, i.e., scleroderma, etc.). Weak tissue fosters impaired resistance against mechanical stress [52].
2. *Mechanical stress* due to increased abdominal pressure contributes to unfold the LES. Causes for increased abdominal pressure and tension forces towards the diaphragm include obesity, constipation (straining), eating behavior (overeating, large meals, food and beverages containing concentrated, artificial sugar; conservatives, E-substances; food (± concentrated sugar) induced post-prandial gastric contractions and spasms, associated with epigastric crampy pain; delayed gastric emptying, nausea and discomfort, repeated vomiting (eating disorder, migraine), lifting of heavy weights (street worker, sports, gym, etc.), diaphragmatic straining forces (singers, actors), and pregnancy [7, 53, 54].
3. *Medical causes:* medications against depression, sleeping disorders, chronic painkiller consumption, regular use of nicotine, alcohol, drugs (cannabis, designer drugs) [7, 24].

All other GERD-related findings are the *manifestations* of LES failure: symptoms, tissues, and structural alterations of the esophagus (stenosis, diverticula, rings, webs) [7, 20, 24, 36].

14.8 CLE as a Marker for LES Failure: Cellular Instead of Endoscopic Pathology

The above functional changes of the esophagus (i.e., the shortening of the lower esophageal sphincter, impaired esophageal body transport function) are paralleled by morphological alterations (lack limos of adequate epithelial integrity and tissue resistance), as assessed by endoscopic resolution: esophagitis, hiatal hernia, increased grades of the distortion of the geometry of the esophago-gastric junction valve (Hill grades I–IV), and increased length of CLE [7, 16–20, 27, 36]. We point out here into a very fascinating topic, which is well described in detail within the book. Use of the larger magnification of the microscope enabled to demonstrate that what has been taken as *gastric cardia* during endoscopy, in fact represents reflux damaged columnar-lined, dilated, sphincter function lacking lower end of the esophagus [7, 11, 17–20]. The *lack limos* of sphincter function induces the reflux which alters the tissue, and CLE develops due to lack limos of normal squamous-lined esophagus. Due to the lack limos of sphincter and esophageal body transport function, the lower end of the esophagus forms CLE-lined folds [10, 11]. These folds are of gastric appearance during endoscopy and *lack limos* of appropriate magnification creates the idea of gastric cardia [10, 11, 15]. But there is a hidden thing behind, there is a lethe, and this lethe can be unfolded if we recognize that we should replace endoscopic pathology by cellular pathology. What is hidden, i.e., *lethe* during endoscopy becomes a-letheia, i.e., unhidden, if we apply the resolution of histopathology. As such, the so-called *gastric cardia*, as assessed by endoscopic resolution, is recognized as columnar-lined, reflux-damaged esophagus, as confirmed by the highly accurate means of histopathology [10, 11, 15, 20]. *As quantum space time unfolds perception, magnification improves our resolution*.

How did all that happen? It happened because physicians obtained biopsies from the so-called cardia, and the histopathology of these biopsies clearly showed that the tissues represented fragments of abnormal distal esophagus [11, 17–20], i.e., CLE, and this experience equals the *lack limos* of normalcy in the words of Hesiod. What does this mean? The endoscopic magnification is not appropriate (lack limos of resolution) for the assessment of the distal end of the esophagus and the proximal limit of the stomach. Why? Because the endoscopic appearance of the proximal stomach and the reflux injured inflamed *dilated distal esophagus* are the same [10, 11]. Interestingly, the same argument convinced Norman Barrett to write his CLE paper [48]. But forgetfulness (lethe) came over us and lack of remembrance avoided us from getting it right again. We have been in a state of *lack limos* of knowledge and awareness regarding the anatomy of the esophago-gastric junction. Correlation of anatomy, histology, histopathology, and esophageal function test contributed to reveal the hidden, i.e., lethe. Numerous studies demonstrated that the lack limos of lower esophageal sphincter (LES) function correlated with increased reflux, length of CLE and BE, and development of cancer [7, 12, 16, 31, 32, 36, 47]. In addition, effective anti-reflux surgery and ablation therapies reversed BE and cancer risk [55–57].

14.9 No CLE Without Reflux

Let us replace endoscopic by *cellular* pathology. If we aim to base our GERD management (diagnosis, grading of disease, therapy, therapy monitoring, cancer prevention) on the histopathology of CLE, we have to be sure that reflux is the only cause for the development of CLE and that the extent of CLE correlates with the severity of GERD. Fortunately, there exists a large body of evidence, which supports the notion that CLE represents a reproducible, sensitive marker for reflux at the cellular level (no CLE without reflux) [11, 12]. Thus, at least by theory, histopathology collects the information, which may serve as the fundamental and most reliable marker for GERD diagnosis, therapy, and follow-up. Those are the facts we have, which indicate that there develops no CLE without reflux.

Following subtotal esophagectomy and reconstruction of the upper GI tract with an esophago-gastric tube anastomosis served to elucidate the morphological consequences or reflux. After the surgery, squamous-lined esophagus connected to the mucosa of the proximal stomach. There existed no sphincter anymore and as a consequence reflux of gastric content into the remnant esophagus occurred. The histopathology of follow-up biopsies demonstrated that the stomach remained normal, and there were no abnormal chances observed within the mucosa of the stomach. In contrast to that, all patients developed CLE within their remnant esophagus, up to 36% developed BE [58, 59].

Following radiofrequency ablation (RFA) stenosis may occur in 2–4% of the cases. This prevents the reflux of gastric juice into the segment of the esophagus above the level of the stenosis. As a consequence, post RFA assessment showed absence of any CLE above the stenosis and CLE and neosquamous epithelium below the level of the stenosis [1, 4, 7].

Numerous studies correlated the presence and length of CLE, BE, and esophageal function [12, 13, 16, 20]. The studies demonstrated that the length and presence of CLE and BE correlated with a distorted geometry of the lower esophagus/diaphragm (hiatal hernia) increased reflux and the dysfunction of the lower esophageal sphincter (length, pressure) [12, 13, 16, 20].

Effective anti-reflux surgery (Nissen fundoplication, LINX system) contributed to foster the regression of BE in 25–30% of the cases [55–57]. Therefore, the parts of the puzzle-evidence are strong and highly convincing to support the notion, that the dysfunction of the lower esophageal sphincter fosters reflux, which in turn manifests in the form of CLE and BE [7].

During GERD, CLE interposes between the normal squamous-lined esophagus and the normal mucosa of the proximal stomach. Chandrasoma and DeMeester coined the term "*squamo-oxyntic gap"* (SOG) for this reflux-induced condition [15]. Their data indicate that the length of the SOG correlates with the severity of GERD. For example, the longer the SOG, the more advanced the stage of GERD and the higher the probability to have BE [12, 13, 15]. However, we still lack accurate correlation between the length of the SOG and esophageal function data (manometry, reflux monitoring). As such our book aims to motivate future clinical science for a better understanding of reflux, GERD, and BE. If these studies will

proof, that SOG characteristics (length, cellular composition) correlate with other markers of the disease (symptoms, esophageal function, cancer risk), the SOG will serve as a novel, reliable, and sensitive marker for reflux, GERD, and BE management [20]. Then we will be allowed to close the diagnostic gap for the benefit of those affected by reflux, GERD, BE and cancer risk, who come to see us to seek medical care [7, 14].

14.10 Is There More Than LES Failure?

Going in line with the ideas of Hesiod, we have seen that the spectrum of GERD phenomena during diagnosis, therapy, therapy monitoring, and follow-up may in fact be seen as different forms of lack limos deficiencies. First, there is the spectrum of deficiencies of esophageal structure and function. Second, we know about the lack limos limitations regarding the level of magnification for the adequate assessment of the disease (endoscopic vs. histopathological diagnosis) [60, 61]. Third, there are the lack limos deficiencies regarding the knowledge of known and still unknown aspects of the disease. We still do not know: what is the normal length and function of the LES at birth and at adolescence. But we know that there are studies showing a max length of 6.0 cm [36–39]. We know that those presenting with shorter length than 6.0 cm all harbor CLE interposed between the normal squamous lining of the esophagus and the normal mucosa of the gastric body [15, 19, 62, 63]. In addition, CLE associates with increased acid exposure of the esophagus [12–16, 20, 62]. These data justify to assume that CLE developed at the cost of functioning LES. Fourth, there exists a lack limos of knowledge of the patients regarding adequate lifestyle, nutrition, and eating behavior to support the treatment of GERD and BE [53, 54]. Thus, reflux appears in the form of multiple *lack limos* phenomena. But there seems to be one more essential driver and cause.

14.11 Failure of Discipline

Hesiod names the very reason and cause of *limos* and *lethe*: he names it the "strife" [33]. According to Hesiod, it seems that strife causes the playground for *lethe* and *limos*. And this observation seems to be of major importance. What kind of strife is he talking about? Approximately 100 years after Hesiod, Heraclitus, and Parmenides created their imaginations of the world. Going in line with Hesiod, Heraclitus also came up with the conclusion that strife represents the underlying cause of every perception. He calls it: polemos! And we recall his saying, where he states: polemos is the father of all things. At this point we have to ask ourselves: what is the strife all about, who are the actors of the strife, of the polemos? A deeper reading reveals the essential understanding of Hesiod's citation: the strife, the polemos between lethe and aletheia, between the hidden and unhidden is the world, is being, is existence, is all, and this all is one (Heraclitus) [11]. And this all equals our reasoning (Parmenides). Within the tensions of the hidden (lethe) and the unhidden (a-letheia),

our reasoning creates the perceptions, which allow us to establish a diagnosis, design a therapy, and conduct therapy monitoring and follow-up [8–11]. The "strife" between *lethe* and *a-letheia* is driven by the *lack limos* of information. And here the circuit closes and continues to push forward. Going in line with Parmenides knowing (Greek: noein) and being (einai) are the same. Furthermore, there exists the strife, battle, confrontation, and dispute between healthy and unhealthy lifestyle aspects. It is well accepted that food and beverages containing concentrated sugar, artificial sugar, conservatives, and E-substances foster the development of reflux, GERD, BE, and esophageal cancer [4, 5, 53, 54]. Due to our culture and eating habits, it is hard for the patients to abandon these foods and beverages. As a consequence, nutrition therapy and diets face the strife between "what is allowed" and "what is not allowed." Such tensions of strife also affect the well-being and the life quality. Is there a way out of the struggle? Well, there is a way and we know we can: Hesiod names the muse, the principle of strict order and discipline. As a consequence, discipline fosters to outbalance the tensions and to achieve balance, health, and well-being.

Taken together, the principle for reflux, GERD, and BE management seems to unhide (*a-letheia*) in the form of discipline for both the physician and the patient [11, 53, 54]. Following strict order and discipline, the physician should accurately diagnose and treat the cause of the disease, i.e., the dysfunction, the failure of the LES, which represents in the form of the CLE-lined squamo-oxyntic gap (SOG) [15, 32]. The patient should follow the recommendations of the physician for diagnosis and therapy [7]. As such, we are aware of the rich value of the legacy of old European reasoning for nowadays medicine and patient care [33, 34].

14.12 Reflux: Normalcy, Abnormality, and Disease

We hope that our journey motivates you to allow a different, histopathology-based perspective towards reflux, GERD, and BE management. As such, histopathology offers the possibility to differentiate between normality, abnormality, and disease (Table 14.2). When compared to symptomatology, endoscopy and function test data, histopathology offers the advantage of an increased resolution, i.e., resolution at the *cellular level* [28–31, 40, 62, 63].

Going in line with the above considerations, CLE represents the histopathological marker for reflux (no CLE without reflux) and may occur with and without symptoms and cancer risk (BE) [1, 2, 10, 47, 63]. Consequently, the presence of symptoms ± cancer risk (BE) or cancer risk (BE) without symptoms defines *disease* (GERD). The finding of BE-negative CLE without symptoms, defines *abnormality*. The absence of any CLE, i.e., squamo-oxyntic gap (SOG) negative individual, defines *normalcy* [4, 15, 63]. Future investigations may contribute to clarify the correlations between histopathology, endoscopy, and function test data. As a consequence, the *multi-* and *interdisciplinary* management will recommend:

Table 14.2 Proposed histopathology-based definition of esophago-gastric junction characteristics

Category	Finding	Consequence
Normalcy (no reflux)	Absence of CLE and symptoms[a]	Prevention against progression (lifestyle measures); follow up EGD[b]
Abnormality (asymptomatic reflux without cancer risk)	CLE without symptoms and cancer risk[c]	Prevention against progression (lifestyle measures); follow up EGD[b]
Disease (GERD)	CLE with symptoms CLE with cancer risk ± symptoms (heartburn etc.)[c]	Therapy of lower esophageal sphincter failure; elimination of cancer risk tissue; therapy monitoring (follow up EGD)

[a]Symptoms without CLE indicate that reflux is not the cause for the symptoms; individuals without CLE have been examined in an autopsy study by Chandrasoma et al., in 2000 [63]
[b]*EGD* esophagogastroduodenoscopy, *CLE* columnar-lined esophagus serves as marker for reflux at the cellular level (no CLE without reflux)
[c]Presence of Barrett's esophagus ± dysplasia defines cancer risk

- Treatment of disease: elimination of symptoms and cancer risk, using lifestyle measures, medical, endoscopic, and surgical therapies.
- Prevention of disease: prevent abnormality (symptom and cancer risk negative CLE) from becoming a disease, using lifestyle measures.
- Normality: in the absence of any CLE, SOG, there is no need for intervention, and prevention may be recommended in order to prevent normality from becoming an abnormality.

Follow-up endoscopies will serve reflux-related management and monitoring.

The histopathology-based differentiation between normalcy, abnormality, and disease may offer an alternative approach for reflux management and cancer prevention [50, 64]. The fact, that individuals without symptoms are considered to be normal and are thus not seen by a physician, explains why there exist no data describing the progression from normalcy to disease, from health to cancer. Such studies would provide enormously valuable information for disease and cancer prevention. As such, Hesiod might have been categorized as having had asymptomatic, Barrett's esophagus negative reflux. Otherwise, he would have reported on complex constellations between gods, goddess, nymphs, and heroes related to bile, acid, and gullet sounds of tube. So, what do we have?

There is a lot we have, and our book presents you the spectrum of new data related to the diagnosis, therapy, and follow-up of GERD and BE. As a consequence, the book summarizes how the individual aspects of the spectrum of manifestations of GERD translate into diagnosis and therapy. The *inter-* and *multidisciplinary* spectrum of contributions include GERD symptomatology, endoscopy, histopathology, endoscopic mucosal resections, transoral and laparoscopic anti-reflux surgeries, the management of Barrett's esophagus (BE), esophageal cancer, palliation therapies, and cancer prevention. Most importantly, the book outlines the relevance of GERD for ear, throat, and nose (ENT) medicine and how

modern GERD management recommends the involvement of ENT into diagnosis and therapy. As such, GERD-positive individuals working as singers and actors will benefit from the interdisciplinary approach.

Taken together, our goal is met if the book fosters a *different* understanding of reflux, GERD, and BE and contributes to improve your daily routine. Fun Do for You!

Acknowledgments The authors thank their families, friends, colleagues, and teachers for their passion, support, and understanding. Otherwise the project would not have been possible. Finally, the authors thank their patients, from whom they were allowed to borrow knowledge and perception, which fostered a deeper understanding of reflux, GERD, and BE.

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GERD Outlook: A Gastroenterologist's Perspective

15

George Triadafilopoulos

Abbreviations

ARMS	Anti-reflux mucosectomy
EART	Endoscopic anti-reflux therapy
GEJ	Gastro-esophageal junction
GERD	Gastroesophageal reflux disease
GERD-HRQL	GERD Health-Related Quality of Life
LARS	Laparoscopic anti-reflux surgery
LESP	Lower esophageal sphincter pressure
PPI	Proton pump inhibitors
TF	Transoral fundoplication

The recent availability and expanding application of many novel diagnostic and treatment modalities have led to a dramatic modernization, both medical and surgical, of the management of patients with gastroesophageal reflux disease (GERD) and its complications and have created a need for multidisciplinary interaction and decision-making that crosses the boundaries of traditional medical or surgical practice. Therefore, there are no gastroenterologists' or surgeons' perspectives, but one, of *precision reflux management* that takes into consideration all aspects of the disease and its manifestations and formulates the best possible approach for each individual patient, that may involve medical, endoscopic, or surgical modalities, alone or in combination (Table 15.1).

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_15

Table 15.1 Ten key questions for precision GERD management

1. Is GERD truly present and validated by endoscopy and/or pH monitoring?
2. Does GERD affect the patient's quality of life?
3. Is there a confounding illness that makes GERD worse?
4. Has pharmacologic therapy been optimized?
5. Is there a sliding hiatal hernia that would require repair?
6. Are GERD complications (i.e., strictures, Barrett's esophagus) present?
7. Are the esophageal structure and function adequate to undertake an endoscopic or surgical intervention?
8. Is the patient treatment-naïve or has failed or inadequately responded to previous therapies?
9. Is there significant obesity present that would be amenable to endoscopic or surgical therapy?
10. Are there extra-esophageal manifestations present, either alone or together with typical GER symptoms?

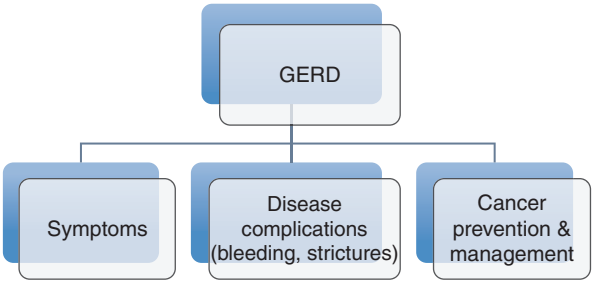

Fig. 15.1 Spectrum of GERD: Clinicians caring for patients with GERD should always consider the symptoms and quality of life (QoL), disease complications (bleeding, strictures, etc.) as well as cancer prevention and management in patients with Barrett's esophagus (BE), dysplasia, and esophageal adenocarcinoma (EAC)

Figure 15.1 highlights the spectrum of GERD seen from the precision reflux management perspective. First and foremost, is the attention to the symptoms, if such symptoms truly reflect abnormal esophageal acid exposure, and to what degree they affect the patient's quality of life, thereby requiring intervention. In the era of increasing recognition of adverse events due to long-term proton pump inhibition (PPI), it is important to establish if such therapy is appropriate and justified [1]. In the patient with refractory GERD, one should examine if pharmacologic management has been optimized and to what degree if there are any confounding illness that would make GERD worse. Although in the modern era of PPI use, disease complications, such as esophageal ulcer bleeding and stricture formation, have become infrequent and are still part of the disease landscape and require expert therapy. Finally, given the rising incidence of esophageal adenocarcinoma, cancer prevention and management of Barrett's esophagus (BE) are essential elements in the initial and long-term management of GERD in all patients but more so in white, obese males [2].

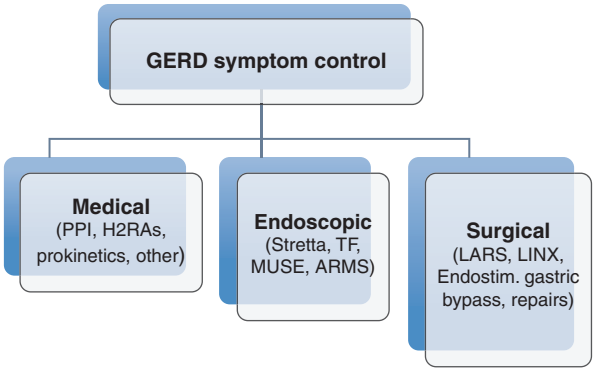

Fig. 15.2 Control of GERD symptoms: Medical (pharmacologic) therapy using proton pump inhibitors (PPI), H2 receptor antagonists (H2RAs), prokinetics, or other agents is cornerstone. For certain, carefully selected patients, endoscopic therapies, such as radiofrequency therapy (Stretta), transoral fundoplication (TF), endoscopic partial fundoplication under ultrasound guidance (MUSE), or anti-reflux mucosectomy (ARMS) may be tried. Laparoscopic options include anti-reflux surgery (LARS), magnetic sphincter implantation (LINX), electrical sphincter stimulation (Endostim), Roux-en-Y bypass for obesity, and hernia repair surgery

Figure 15.2 outlines the various elements of GERD symptom control. Pharmacologic treatment may require therapies beyond PPIs, such as H2 receptor antagonists, prokinetics, or even low-dose tricyclic agents. Although the symptoms of heartburn and acid regurgitation are highly disease specific, they are imperfect and other diagnoses need to be considered. In a patient using PPIs, it is useful to ask what happens if these drugs are transiently discontinued. Under such circumstances, *bona fide* patients with GERD quickly develop heartburn and acid regurgitation (or other more atypical symptoms) while patients with other diagnoses tend to tolerate PPI abstinence for quite some time. The latter group of patients should not be considered as good candidates for invasive procedures but instead be evaluated further to define the underlying reason for their symptoms. Extra-esophageal symptoms, such as noncardiac chest pain, cough, asthma, and hoarseness, are less responsive to any interventions and proof that GERD is their underlying cause and is advised in order to maximize gains.

The best way to validate the diagnosis in a patient with a negative endoscopic examination is ambulatory esophageal pH monitoring that is performed either using a transnasal catheter (impedance/pH) or wirelessly by placing the Bravo pH probe [3]. These tools quantify esophageal acid exposure and are invaluable in establishing the diagnosis of GERD and, further, assessing its magnitude, occurrence in the upright or supine position, and relating acid reflux events to symptoms. If the pH/impedance study is negative, other possibilities, particularly achalasia, esophageal spasm, or gastroparesis, need to be considered. Yet, even if the pH/impedance study is positive, overlap syndromes may occur. For example, in a recent study, pathologic acid reflux was found in 44% of patients with esophageal dysmotility/achalasia and 73% of patients with gastroparesis [4]. Another important question to be addressed

is the presence of regurgitation, or "volume" reflux, particularly while patients are on PPI therapy. Its presence suggests more severe, mostly, supine GERD and also a higher likelihood of underlying hiatal hernia, complicated disease (i.e., Barrett's esophagus), and respiratory manifestations. Regurgitation is a key point in the discussion of pursuing endoscopic and surgical therapies for GERD [5].

Endoscopic anti-reflux therapy (EART) intends to address three key issues: First, the need to eliminate symptoms that are not completely controlled by PPIs; second to eliminate long-term PPI use in those patients who, although well-controlled pharmacologically, are concerned about drug-related adverse events; and third to minimize the need for laparoscopic anti-reflux surgery (LARS) and its complications [6]. Over the past 15 years, these clinical issues have become increasingly prevalent and clinically significant, thereby expanding the potential applicability and clinical value of EART. The *GERD treatment gap* represents the 25–30% of patients with refractory GERD who are not willing to undergo conventional, albeit laparoscopic, fundoplication, mostly because they are afraid of potential long-term side effects, such as difficulty with belching, bloating, and dysphagia [7]. It has also become clear that not all patients with GERD are suitable candidates for such an option and that a careful objective evaluation is needed in order to phenotypically characterize the disease and tailor therapy, aiming at producing the best long-term efficacy and safety.

Currently, there are four EART options available. Radiofrequency therapy of GEJ (Stretta) has the best long-term data [8]. The transoral fundoplication (TF) device creates molding of the GEJ through endoscopic placement of polypropylene suture material; its short-term efficacy and safety have been recently demonstrated in controlled clinical trials. The MUSE™ endoscopic stapling system is a recent technique that creates an endoscopic partial fundoplication under ultrasound guidance, but clinical data is still scant. More recently, the use of conventional endoscopic dissection tools to perform anti-reflux mucosectomy (ARMS) has been reported from Japan.

Several minimally invasive options have entered the realm of surgical GERD management aiming at minimizing the adverse events encountered with laparoscopic anti-reflux surgery, while providing an effective anti-reflux barrier, and they include the magnetic sphincter augmentation (LINX), electrical stimulation of the lower esophageal sphincter (Endostim), gastric bypass surgery in patients with obesity, and, if needed, laparoscopic surgical repairs [9].

Although PPI therapy remains essential in management, the careful assessment of complications, such as strictures or BE, defines the need for other modalities (Fig. 15.3). Esophageal structure is best assessed by endoscopy, first to exclude other conditions (i.e., other forms of esophagitis or cancer), and to carefully define mucosal integrity, ruling out dysplastic Barrett's esophagus that will require attention prior to any endoscopic or surgical therapy for GERD being applied [10]. In order to provide useful information, endoscopy requires attention to the gastroesophageal junction (GEJ) at various levels of air distention, forward and retrograde viewing, and a meticulous detailing of the mucosa (Fig. 15.4). If the distance of the GEJ from the incisors does not vary significantly with insufflation, one can expect

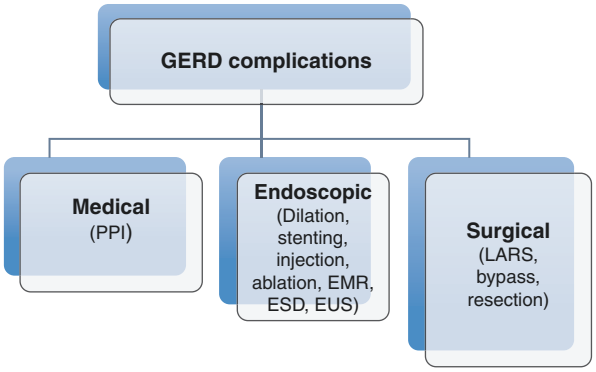

Fig. 15.3 Management of GERD complications. The use of proton pump inhibitors (PPI) remains an adjunctive and important long-term therapy. Endoscopic interventions aim at relieving dysphagia (balloon or wire/bougie dilation, temporary stenting), Barrett's esophagus (BE) ablation and/or endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD). Endoscopic ultrasound (EUS) may be used to clarify the nature of a stricture

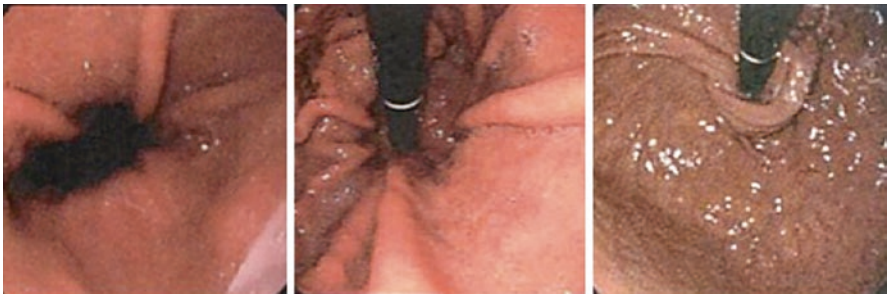

Fig. 15.4 Assessment of the gastro-esophageal junction (GEJ). (**a**) Antegrade view revealing a medium-sized sliding hiatal hernia. (**b**) Retroflexed view of the cardia showing the hernia. (**c**) Retroflexed view of the cardia showing changes of a well-positioned Nissen fundoplication

wall fibrosis and esophageal foreshortening. Fluid pooling, stricture, or tissue nodularity imply atony and complicated disease and are expected to be associated with suboptimal endoscopic or surgical outcomes. Retroflexed views of the cardia during endoscopy are essential not only to confirm the type and size of the hernia but also to assess the GEJ using the Hill classification, a grading system that is easy to learn and has been used and validated for over 20 years [11]. The presence, type, and dimensions of a "sliding" hiatal hernia in need of repair and the underlying esophageal structure and function need to be evaluated. Classic "para-esophageal" hernias readily disqualify from endoscopic intervention. The same is true for "mixed" hernias that are typically large enough and fixed to lend themselves to a successful endoscopic repair. On the other hand, properly assessed sliding hernias that are less than 3 cm in length could be amenable to transoral fundoplication (TF). Available evidence thus far has questioned the feasibility and efficacy of the other endoscopic modalities if the hiatal length exceeds 2 cm.

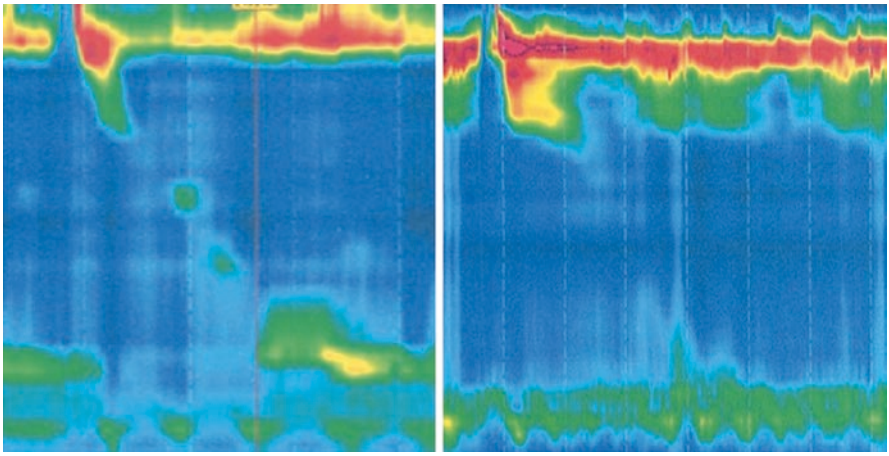

Fig. 15.5 High-resolution esophageal manometry images highlighting ineffective esophageal motility (IEM). (Left panel): Fragmented peristalsis defined as frequent (≥50%) swallows with large (>5 cm) defects in the 20-mmHg isobaric contour; (Right panel): Failed peristalsis with a DCI ≥450 mmHg s cm

Functional assessment mainly aims to exclude achalasia or other forms of severe peristaltic failure that would impede the placement of a magnetic sphincter or a 360° fundoplication and may favor instead a partial 270° (Toupet) fundoplication or a Collis gastroplasty. It is debatable to what degree ineffective esophageal peristalsis (IEM) and other lesser disorders of function detected by high-resolution manometry (HRM) serve as contraindications to surgery or endoscopic management (Fig. 15.5). As a general rule, the creation of a tight anti-reflux barrier may aggravate dysphagia and difficulties with throat clearance and any invasive option needs to be carefully examined and individualized. In general, if a patient with GERD is a candidate for anti-obesity surgery, the performance of Roux-en-Y bypass is the best surgical option. Sleeve gastrectomy is less likely to be associated with complete control of GERD symptoms, but if such symptoms occur postoperatively, radiofrequency therapy of EGJ is feasible and effective [12].

There are very limited data in patients who have previously undergone either endoscopic or surgical therapies for GERD and present with refractory symptoms. Stretta can be performed repeatedly or in a patient post anti-reflux surgery but not after magnetic sphincter implantation, but there is no published data on its efficacy. In a patient presenting with recurrent GERD after anti-reflux surgery, the degree of wrap displacement, if any, plays an essential role in decision-making. If present, there is no role for EART and surgical repair is the only option [13]. Revisional anti-reflux surgery is always more challenging to perform and its outcomes are considered less robust than those of the initial intervention. The use of mesh to close large hiatal defects that contributed to prior failure remains controversial and needs to be individualized. Finally, patients with prior esophageal injury or those with complicated disease, (i.e., long peptic strictures) that are resistant to medical therapy lone or in combination with temporary endoscopic stenting, may require esophagectomy

instead of EART or anti-reflux surgery. The presence of esophageal stricture calls for endoscopic management aiming at excluding malignancy, and expanding and maintaining the luminal diameter of the esophagus, thereby improving dysphagia. Sometimes temporary stenting facilitates long-term management (Fig. 15.6).

The recognition of BE requires further detailed assessment to exclude dysplasia, using high-definition white light endoscopy (HD-WLE), narrow-band imaging (NBI), in vivo confocal microscopy, and Seattle protocol biopsies. Identification and endoscopic resection of mucosal abnormalities are critical in managing dysplastic BE because these areas may harbor esophageal adenocarcinoma (EAC) [14]. Endoscopic eradication therapy (EET), that is, the resection of visible lesions followed by ablation, is now well established as a first-line treatment option in subjects with BE-related dysplasia and mucosal adenocarcinoma (Fig. 15.7) [15, 16]. EET however has raised two concerns. First, is the potential persistence of undetected

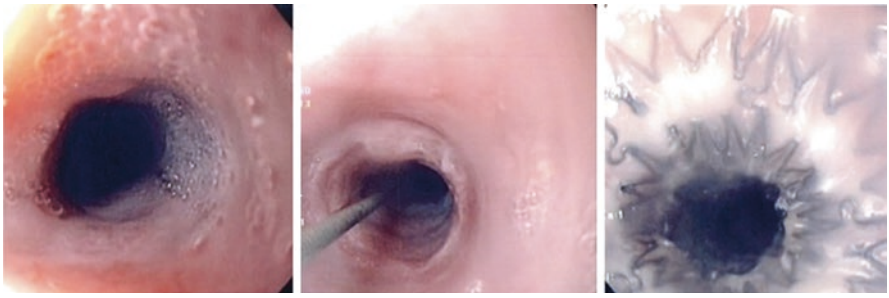

Fig. 15.6 Peptic stricture management. (**a**) Benign appearing mid to distal esophageal stricture that would not allow the passage of the endoscope. (**b**) Wire-based dilation using Savary bougies. (**c**) Endoscopic appearance of a temporary metal stent traversing the stenosis in order to relieve dysphagia

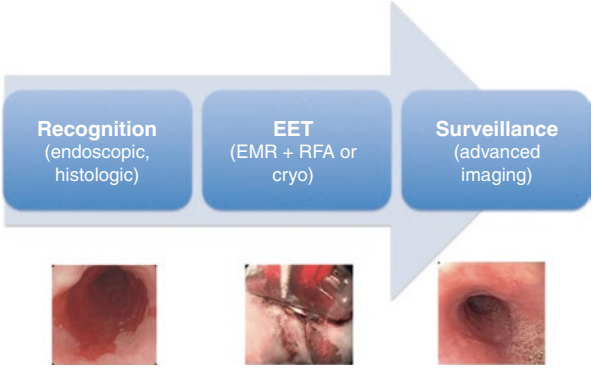

Fig. 15.7 Role of endoscopy in Barrett's esophagus (BE). (**a**) Endoscopy allows recognition and classification of BE and proper histologic diagnosis. (**b**) Endoscopic eradication therapy (EET) ablates the dysplastic mucosa and the surrounding intestinal metaplasia. (**c**) Endoscopic surveillance of the esophagus after ablation usually involves advanced imaging techniques (i.e., volumetric laser endomicroscopy) to detect buried metaplasia or dysplasia

subsquamous BE mucosa (buried BE) that may progress to adenocarcinoma by escaping conventional endoscopic surveillance [17]. Second concern is the rare but documented risk of recurrent BE with dysplasia or adenocarcinoma [18]. Volumetric laser endomicroscopy (VLE) allows rapid visualization of the esophageal wall layers within a few minutes using a laser probe mounted on a balloon. Such rapid scanning of large surface areas of the lamina propria and submucosa with excellent resolution and deeper penetration reliably and safely images the distal esophagus in BE after EET [19] and may accurately to allow targeted tissue acquisition even in ablation-naïve BE patients [20].

Laparoscopic anti-reflux surgery (LARS) is usually preferred in patients with large hiatal hernia, para-esophageal hernia, previously failed EART, in patients with pulmonary manifestations of GERD and in those with Barrett's esophagus resistant to EET. Roux-en-Y bypass surgery is preferred in obese patients with GERD while esophagectomy is reserved for those BE patients with invasive cancer (Fig. 15.8).

In summary, the clinical and phenotypic complexity of GERD requires a detailed, multimodality diagnostic evaluation prior to decision-making for pharmacological, EART or surgical therapies. An individualized selection has to be based on symptoms, clinical presentation, proper disease definition, therapeutic objectives, and available local endoscopic and surgical expertise. As these novel endoscopic and laparoscopic technologies evolve and mature and long-term data becomes available, decision-making will remain in flux but best done at multidisciplinary esophageal centers of excellence.

Compliance with Ethical Standards

Conflict of Interest: The author has equity position with Mederi Therapeutics, C2 Therapeutics, and EndoStim.

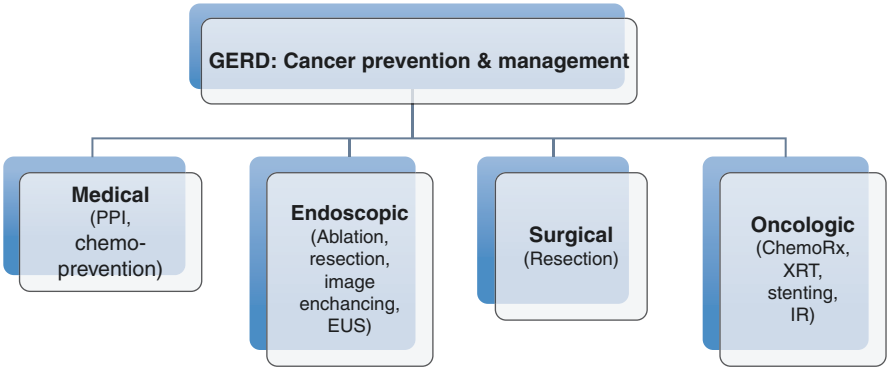

Fig. 15.8 Cancer prevention and management strategies in GERD. Proton pump inhibition (PPI) and/or other agents (i.e., aspirin, statins, and NSAIDs) may have a chemoprevention role in patients with Barrett's esophagus (BE). Advanced endoscopic imaging may identify areas of dysplasia in BE and facilitate ablation or resection of dysplasia and early neoplasia, while endoscopic ultrasound (EUS) facilitates staging. Surgical management involves resection for cancer, while oncologic approaches involve chemotherapy, radiation therapy (XRT), and palliative stenting. Interventional radiologic (IR) techniques assist in tumor staging

Human and Animal Rights and Informed Consent: This chapter does not contain any studies with human or animal subjects performed by the author.

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Outlook for the Management of Gastroesophageal Reflux Disease (GERD): No Esophagus Stands Alone

16

Martin Riegler and Sebastian F. Schoppmann

Dear reader,

At this point, we may summarize the novelties presented in the book and suggest their relevance for future developments. The team of outstanding and highly reputed expert authors orchestrated a fascinating spectrum of open-minded chapters pointing out that the management of gastroesophageal reflux disease (GERD) and Barrett's esophagus (BE) *should consider* the embryological, anatomical, physiological, histological characteristic, and properties of the esophagus during well-being and during disease. As a consequence, these qualities define the requirements, which should be met, and can be met, as we have demonstrated, by modern GERD management.

16.1 Multidisciplinary Management

Due to the anatomy of the esophagus, reflux affects multiple organs and tissues including the diaphragm, chest, throat, ears, mouth, tongue, nose, teeth, lips, lungs, heart, head, neck, and eyes. Maybe it also may affect thyroid function via the vagal nerve mediated reflexes. Thus, GERD management requires a multidisciplinary approach. As a consequence, the esophagus connects people, the esophagus connects experts, and the esophagus may be the cradle for true (and not superficial) friendships and cooperation. As outlined in the book, the esophagus brings together people coming from different fascinating specialities, and every speciality describes

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S. F. Schoppmann, M. Riegler (eds.), *Multidisciplinary Management of Gastroesophageal Reflux Disease*, https://doi.org/10.1007/978-3-030-53751-7_16

his or her individual image of GERD and BE, and thus aids to orchestrate a novel entire image of the disease, the *Gesamtkunstwerk*. Thus, the first lesson learnt from this book says: management of GERD and BE should be multidisciplinary because together we are strong and no physician is an island, no physician stands alone, *no esophagus stands alone*. As such, multiple aspects of GERD diagnosis and therapy are taken within the book.

16.2 GERD Defined at the Cellular Level

Our novel understanding demonstrates that GERD and BE result from the failure of the lower esophageal sphincter and should be defined at a cellular level. Since 30 years, the pathologist *Para Chandrasoma* demonstrates that GERD can be assessed at the cellular level [1, 2]. Only few groups were convinced of his concept and included it into their clinical routine [3–8]. Fortunately, his efforts are now gaining increased acceptance and may help to positively turn the tables in GERD management [9]. Thus, supporting this concept, the US expert gastroenterologist *Stuart Spechler* recently admits, that cardiac mucosa is abnormal, results from reflux, and represents the precursor for Barrett's esophagus [9]. As outlined in this book, reflux induces a sequence of cellular changes, which can be assessed and followed by the histopathology of biopsies obtained from the lower esophagus and the squamocolumnar junction. Briefly, reflux induces the replacement of squamous lined by columnar-lined esophagus (CLE). Thus, the so called *squamo-oxyntic gap* (SOG) develops and represents a highly specific histologic marker for reflux. The SOG interposes between the normal squamous-lined esophagus and the oxyntic mucosa of the proximal stomach. The book nicely describes how the qualities of the squamo-oxyntic gap (length, cellular composition) associate with other typical features of GERD including dysfunction of the lower esophageal sphincter, hernia formation, esophagitis, Barrett's esophagus, development of dysplasia, and cancer.

16.3 Future GERD Management

Going in line with this book, modern GERD management is *multidisciplinary* and follows an *individualized*, *tailored* approach including the following algorithm:

Patient history assesses the reasons for the impairment of life quality and well-being (symptoms, requirement for medical therapy, cancer risk, family history, etc.)

Endoscopy, histopathology, and esophageal function tests (manometry, reflux monitoring) assess the size of lower esophageal sphincter dysfunction, cancer risk.

Therapy aims to fix the lack of function and normalcy by tailored therapy: lifestyle, medical, interventional (endoscopic resection), surgical management (anti-reflux surgery), and surgical oncology.

Follow-up makes sure that life quality and well-being are maintained, i.e., absence of symptoms and cancer risk.

Here we want to thank the authors and their families (wives, husbands, kids) for their passion, humility, and respect required for the preparation of the chapters. We thank Springer for being allowed to publish the book. Finally, we thank you, dear reader, that you take your time sharing with us these fascinating aspects regarding the management of GERD and BE.

Taken together, the book is all about us, about the human being, about the way we live, think, eat, drink, and exist, and how we deal with *our* nature. May the outlook motivate you to orchestrate a positive GERD management and have fun at do (fundo*plication*) and enjoy your life, stay tuned, resist group think and despotism and allow yourself to lively up yourself, NOW!

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